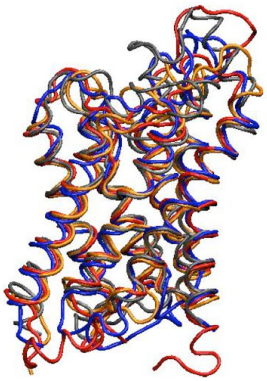
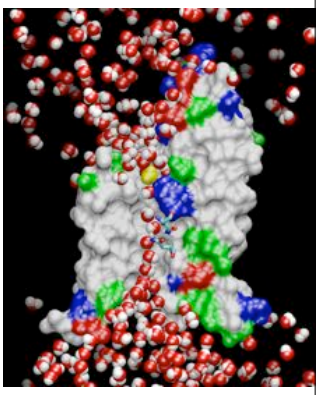
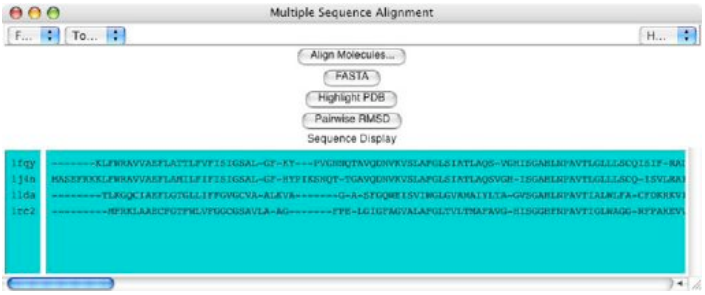
Sequence and Structure Alignment
- Illustrated for the Water Channel Aquaporin





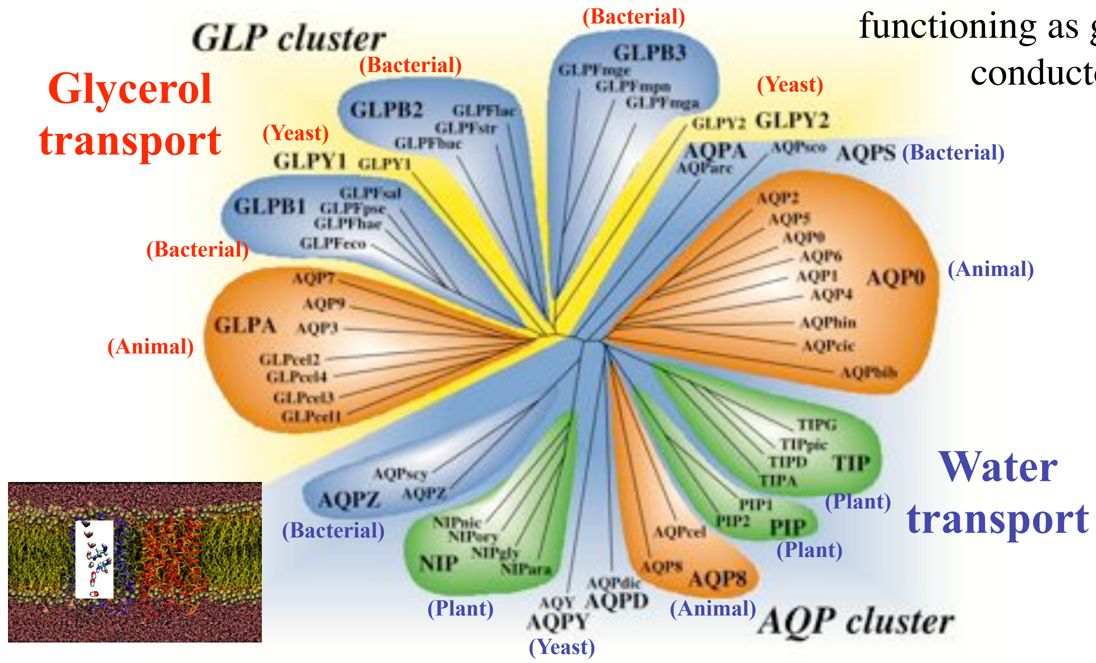


Physical Bioinformatics - A Case Study

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.

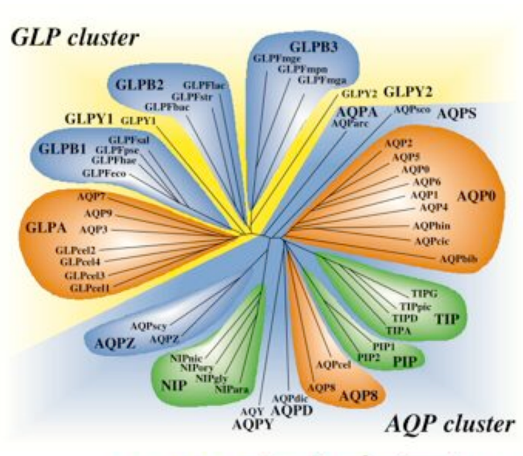
The Aquaporin Superfamily

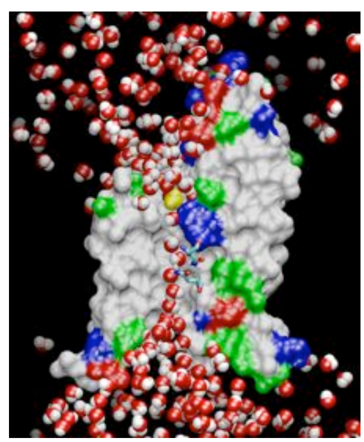
aquaporins are also functioning as gas conductors



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

Aquaporin Function and Human Aquaporins





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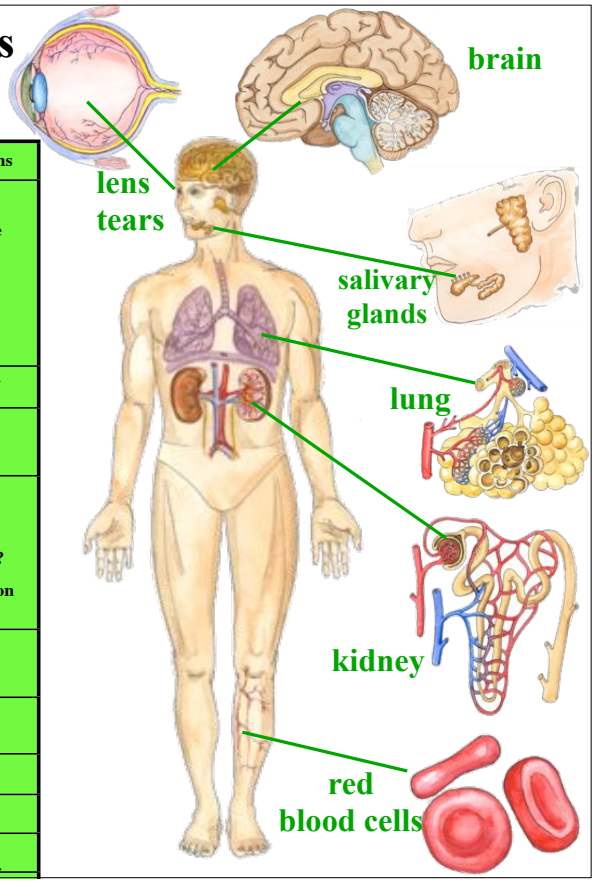
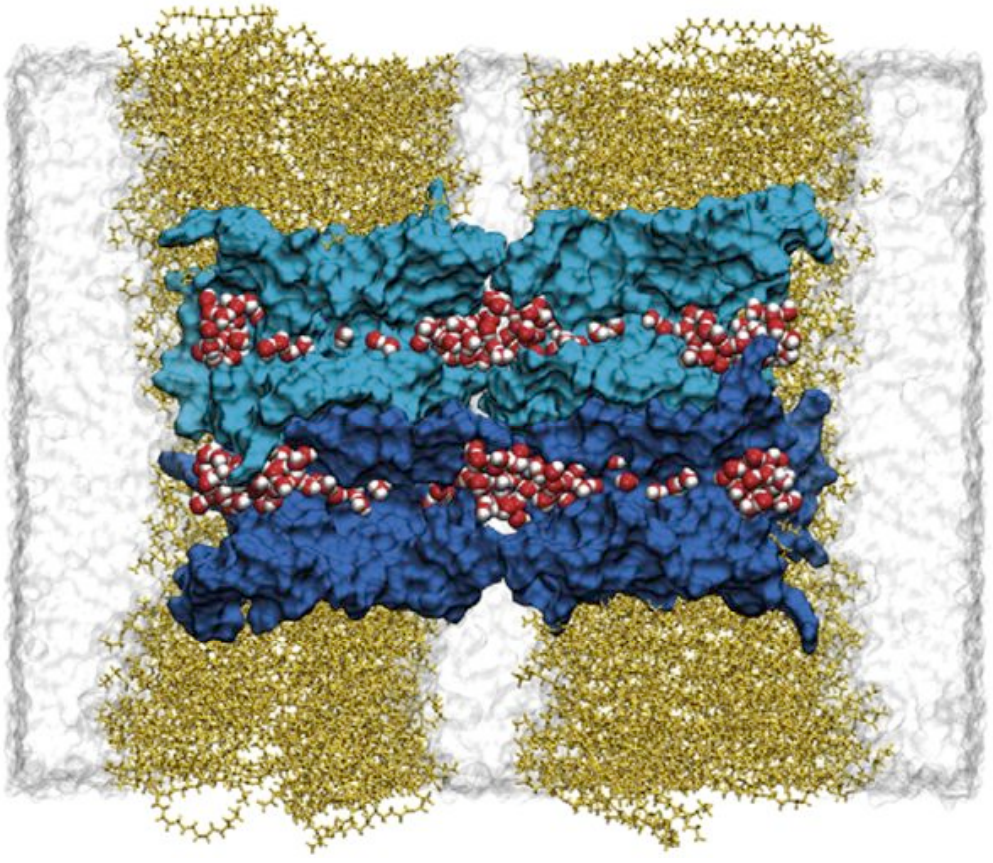
AQP1_HUMAN ---RNDLADGVNSGQGLGIEIIGTLQLVLCVLATTDR-RRRDLGGSAPLAIGLSVALGHLLAIDYTGCGI   191
AQP2_HUMAN ---VNALSNSTTAGQAVTVELFLTLQLVLCIFASTDE-RRGENPGTPALSIGFSVALGHLLGIHYTGCSM   183
AQP3_HUMAN GIFATYPSGHLDMINGFFDQFIGTASLIVCVLAIVDPYNNPVPRGLEAFTVGLVVLVIGTSMGFNSGYAV   214
AQP4_HUMAN ---VTMVHGNLTAGHGLLVELIITFQLVFTIFASCDS-KRTDVTGSIALAIGFSVAIGHLFAINYTGASM   212
AQP5_HUMAN ---VNALNNNTTQGQAMVVELILTFQLALCIFASTDS-RRTSPVGSPALSIGLSVTLGHLVGIYFTGCSM   184
AQP6_HUMAN ---INVVRNSVSTGQAVAVELLLTLQLVLCVFASTDS-RQTS--GSPATMIGISWALGHLIGILFTGCSM   195
AQP7_HUMAN GIFATYLPDHMTLWRGFLNEAWLTGMLQLCLFAITDQENNPALPGTEALVIGILVVIIGVSLGMNTGYAI   225
AQP8_HUMAN -AAFVTVQEQGQVAGALVAEIILTTLLALAVCMGAIN--EKTKGPLAPFSIGFAVTVDILAGGPVSGGCM   209
AQP9_HUMAN HIFATYPAPYLSLANAFADQVVATMILLIIVFAIFDSRNLGAPRGLEPIAIGLLIIVIASSLGLNSGCAM   215
GLPF_ECOLI GTFSTYPNPHINFVQAFAVEMVITAILMGLILALTDDGNGVPRGPLAPLLIGLLIAVIGASMGPLTGFAM   202
     ruler ...180.......190.......200.......210.......220.......230.......240....
```

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.





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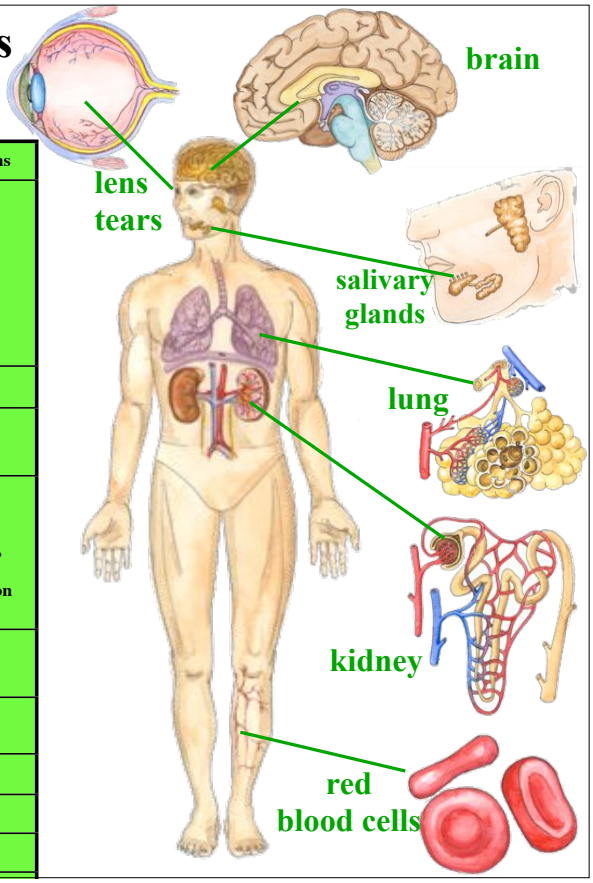
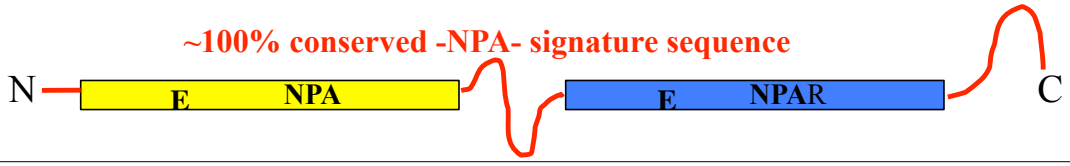


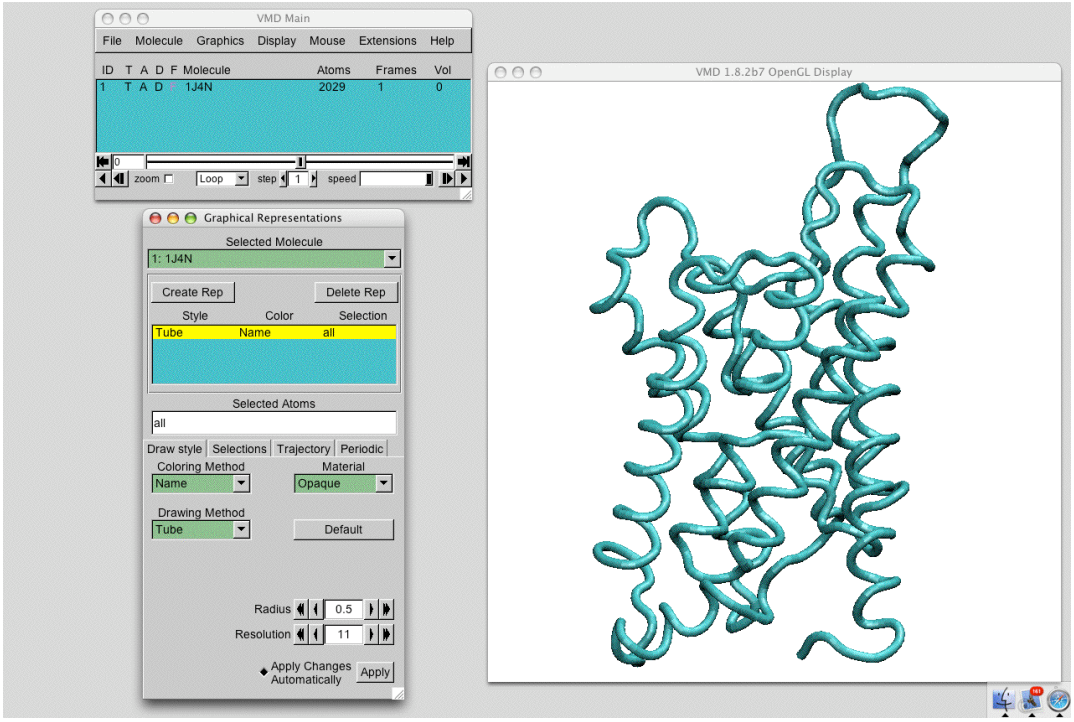
Functionally Important Features of Aquaporins

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

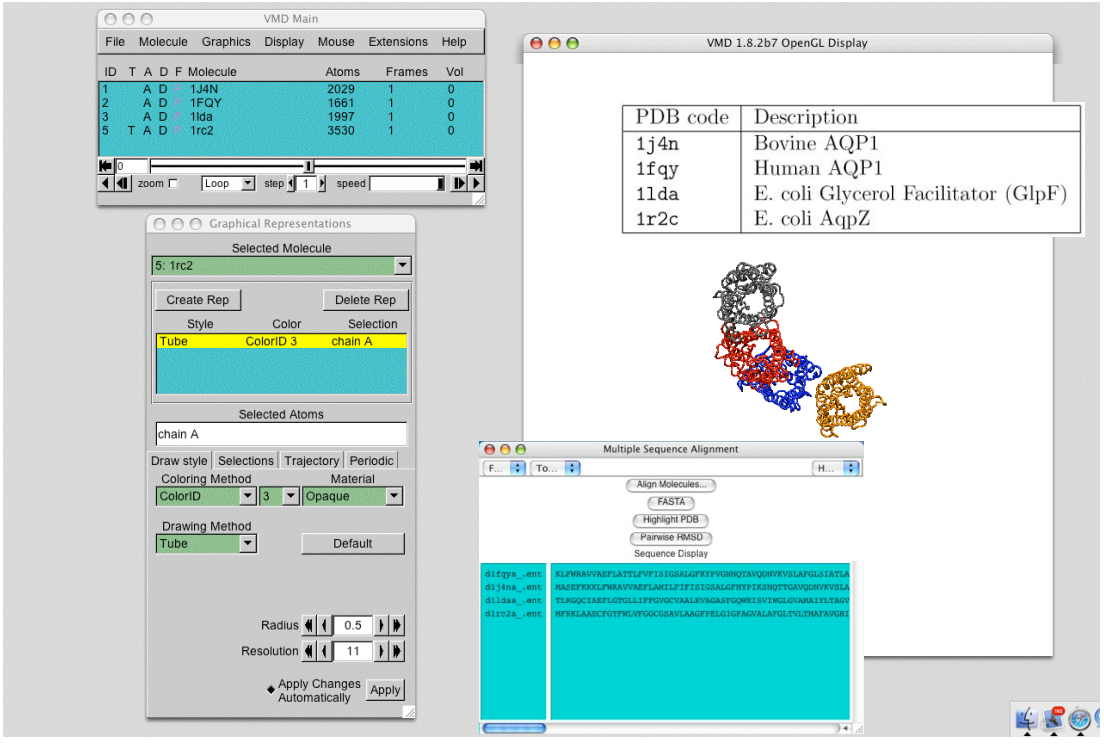
Aquaporins of known structure:
GlpF – E. coli glycerol channel (aquaglyceroporin) – Fu, et al., Science (2000)
AQP1 – Mammalian aquaporin-1 (pure water channel) -Sui et al, Nature (2001)
AQP1 - Bovine - Murata et al, Nature (2000)
AQPZ - E. coli water channel - Savage et al, PLOS Biol (2003)



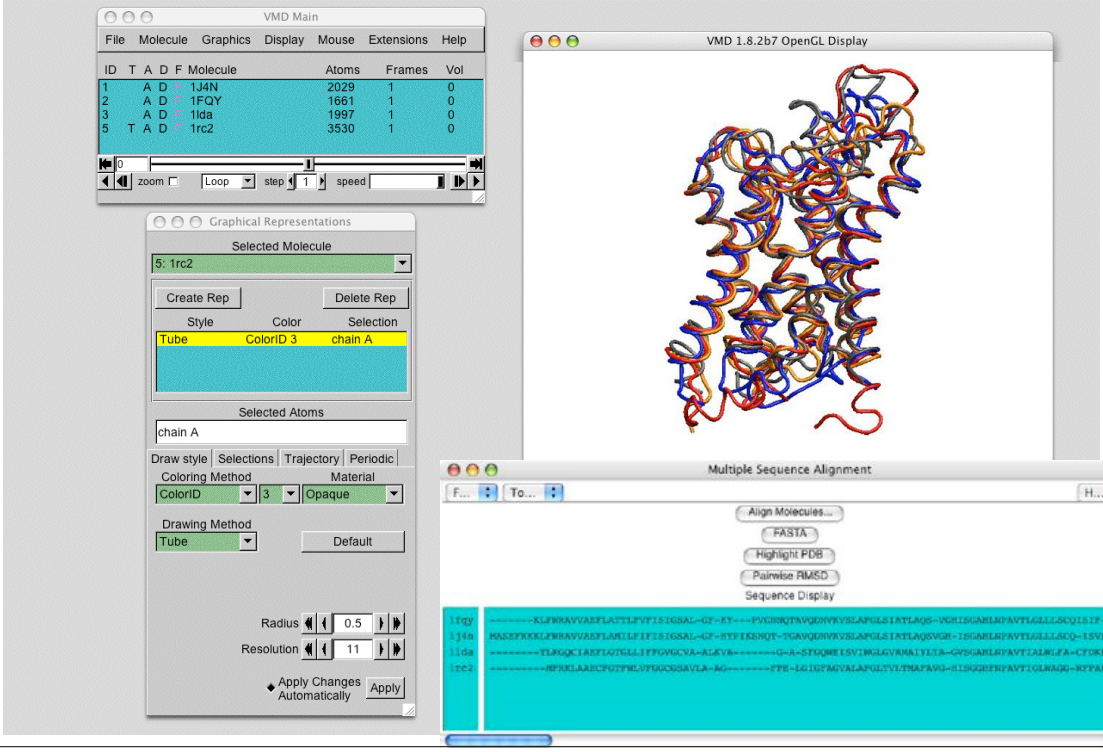
Load Aquaporin 1J4N into VMD



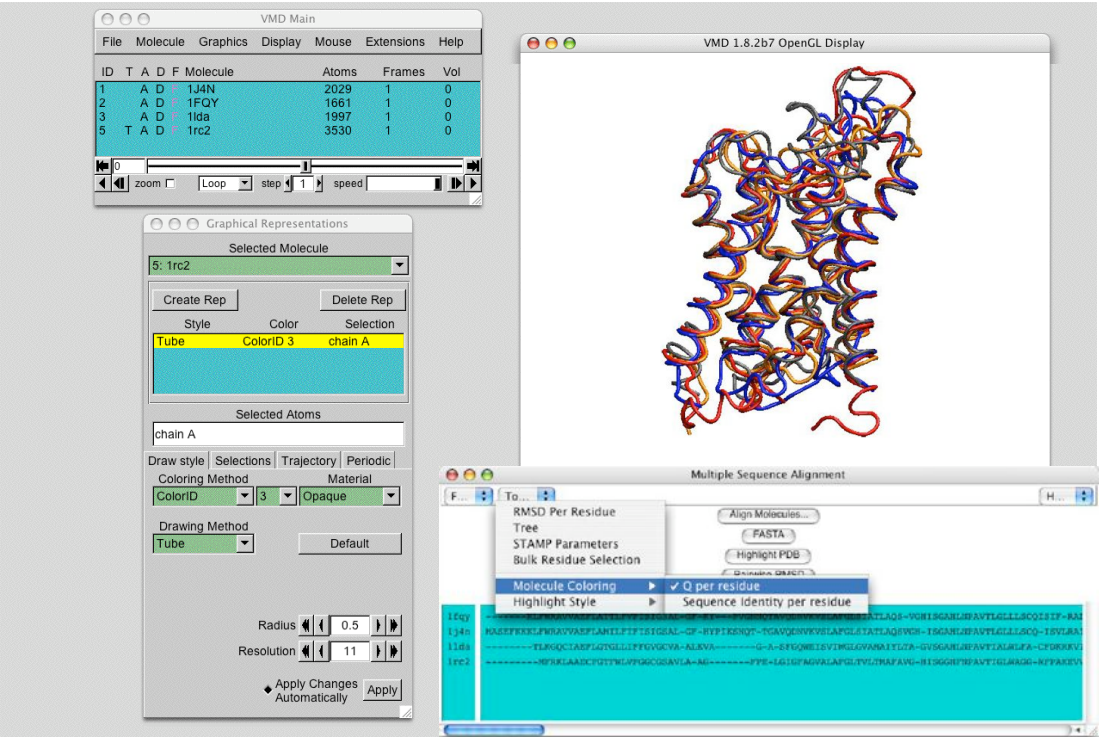
Load Aquaporins 1j4n, 1fqy, 1lda, 1rc2 into VMD



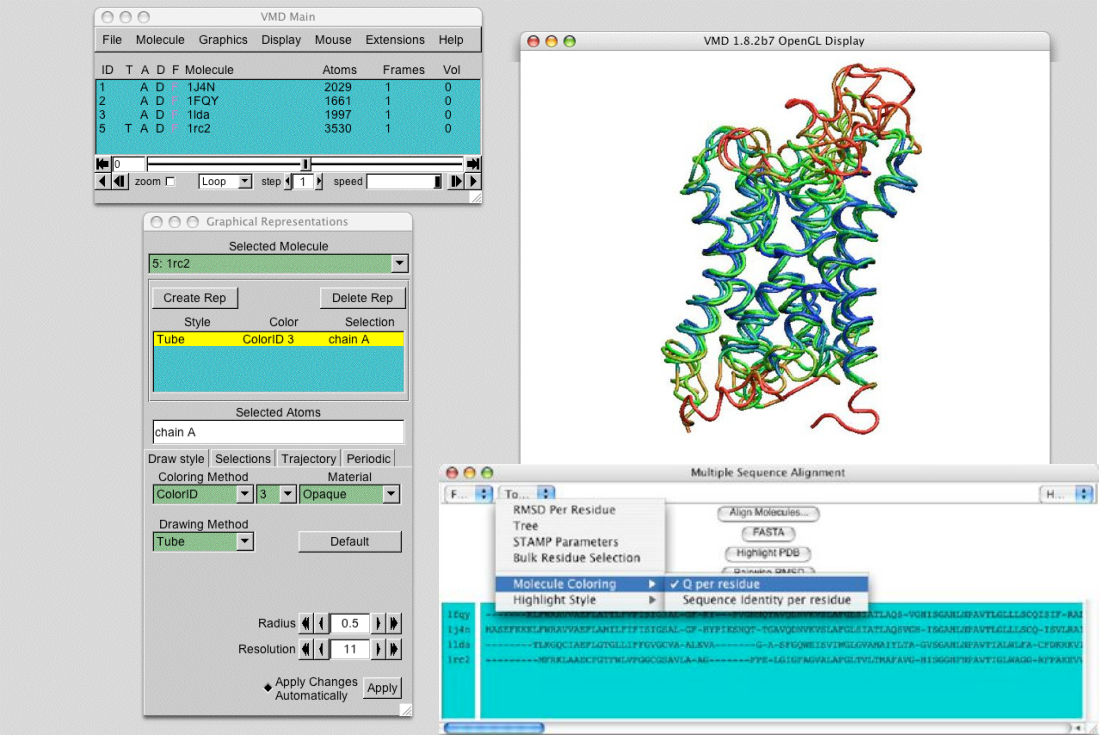
Aligning Structures and Sequences



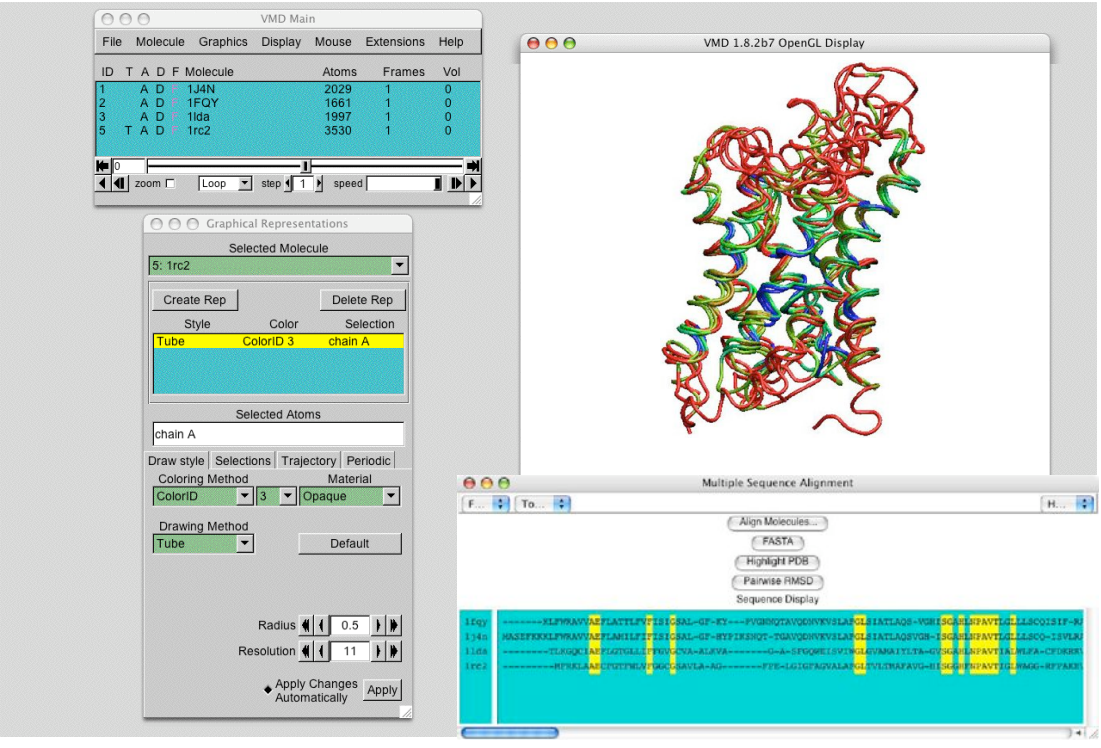
Comparing Structures by Similarity - Q Value



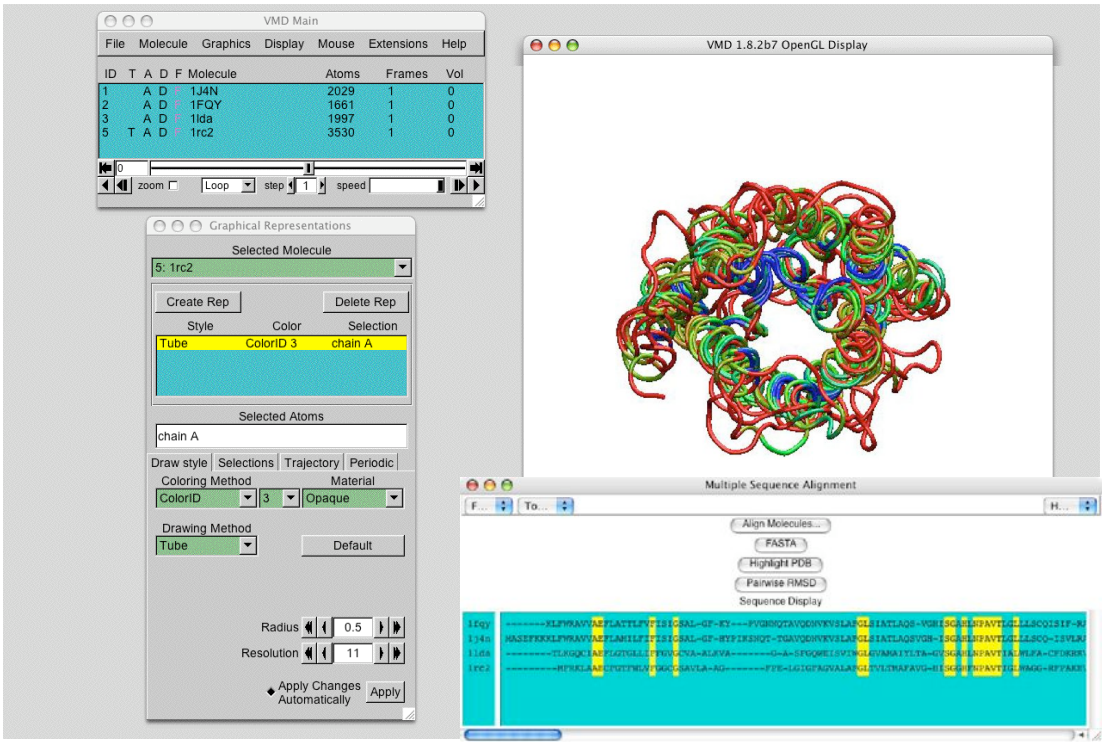
Comparing Structures by Similarity - Q Value



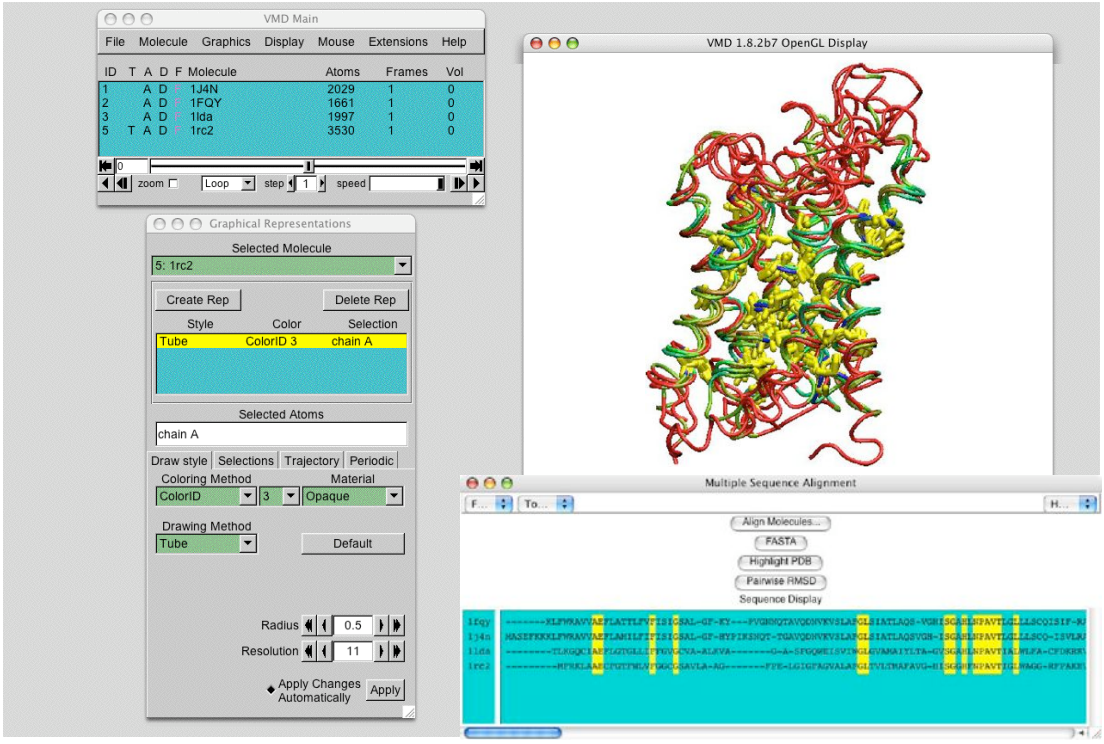
Exhibiting Sequence Identity - Side View



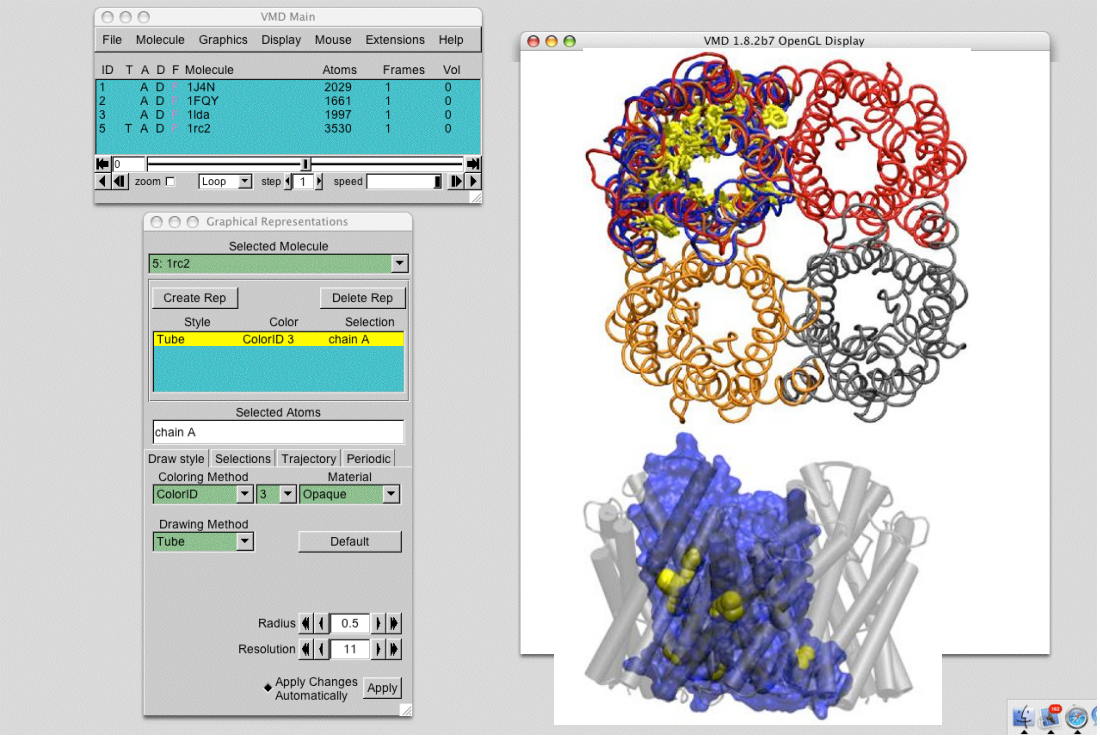
Exhibiting Sequence Identity - Top View



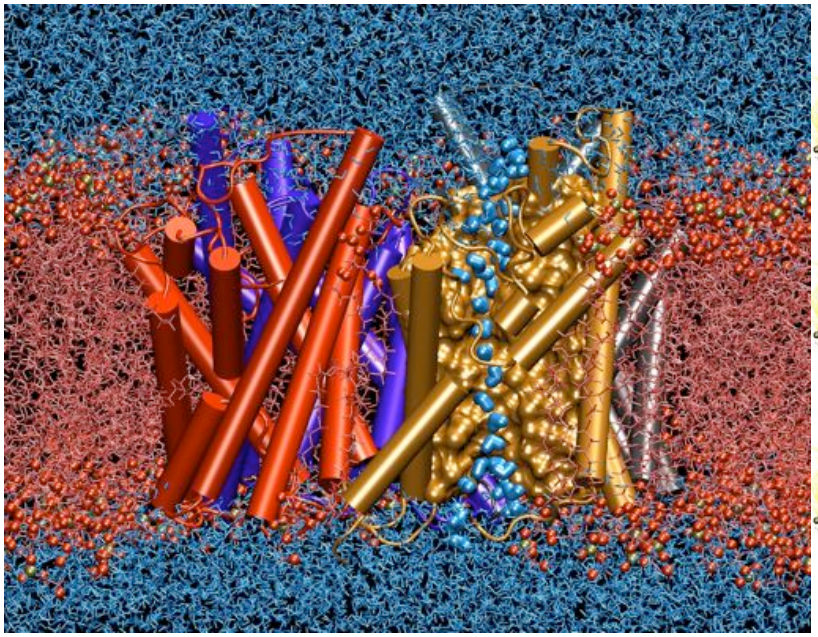
Showing Conserved Residues - Monomer

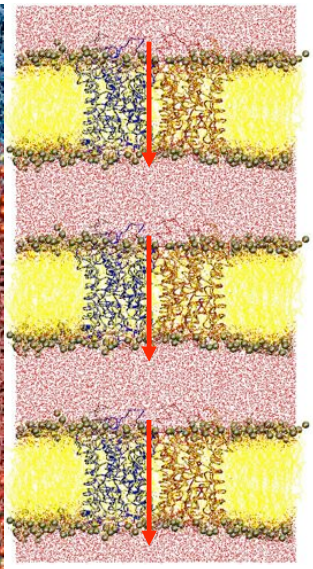


Showing Conserved Residues - Tetramer



Water Transport in Aquaporins



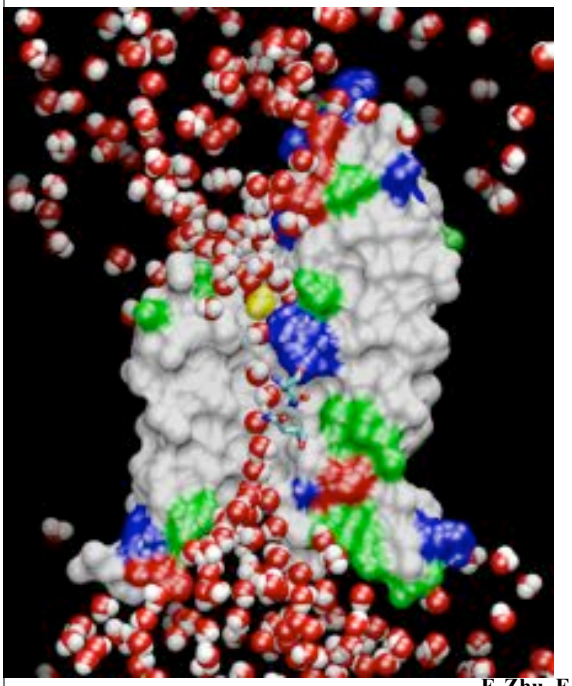


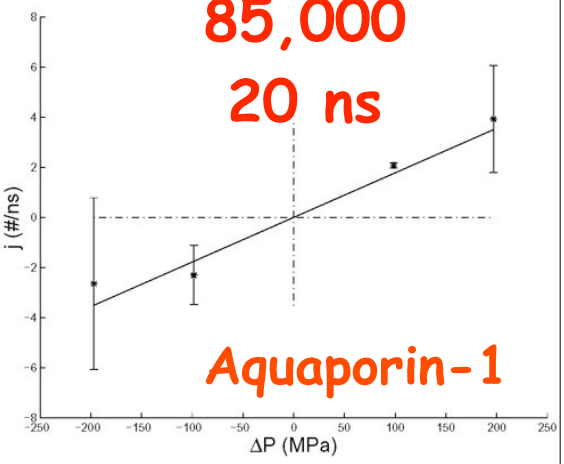
100,000 atoms

Simulation:

Apply constant force on bulk water molecules

Osmotic permeability of water channels

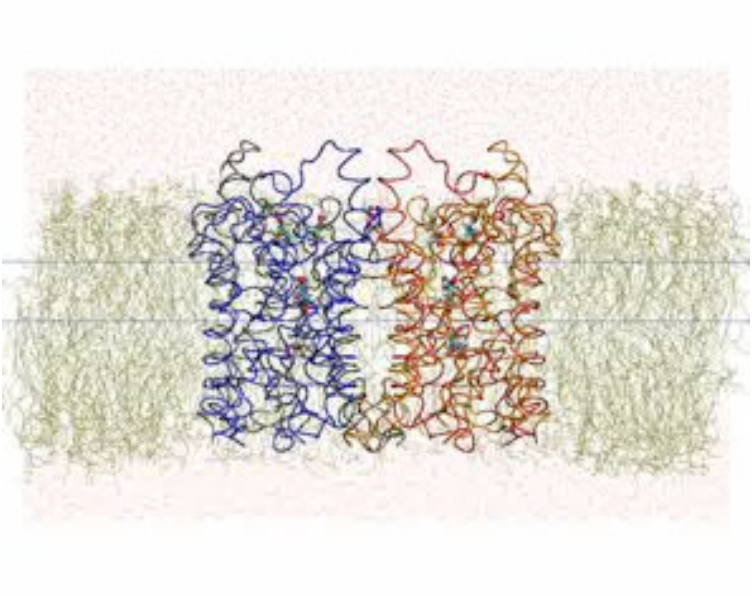


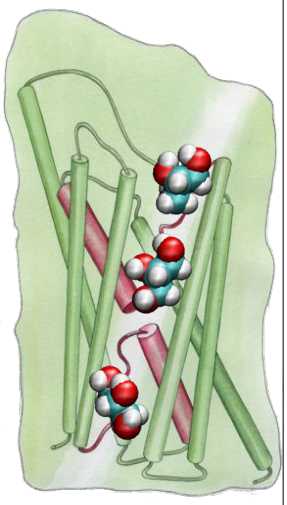


p_f: 7.0 ± 0.9 × 10^{-14} cm^3/s
Exp: 5.4 – 11.7 × 10^{-14} cm^3/s

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

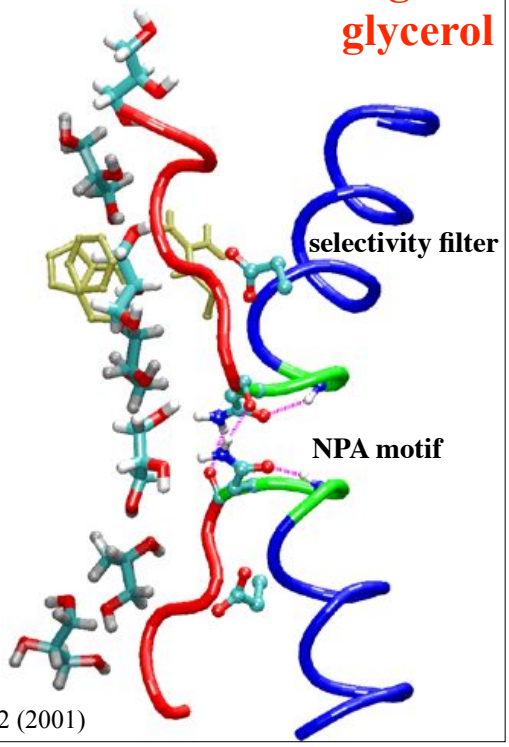




M. Jensen, E. Tajkhorshid, K. Schulten, *Structure* **9,** 1083-1092 (2001)

Glycerol Conduction

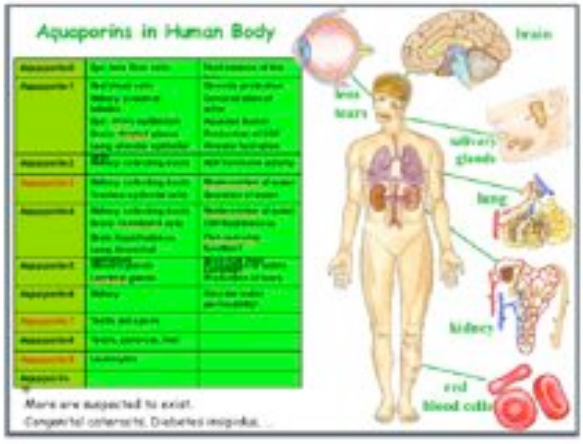
Inverted helices guide glycerol



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

University of Illinois at Urbana-Champaign
NIH Resource for Macromolecular Modeling and Bioinformatics
Beckman Institute

Aquaporins



VMD Developers:
John Stone
Dan Wright
John Eargle
Fatemeh Khalili
Elizabeth Villa
Emad Tajkhorshid
Brijeet Dhaliwal
Zan Luthey-Schulten

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