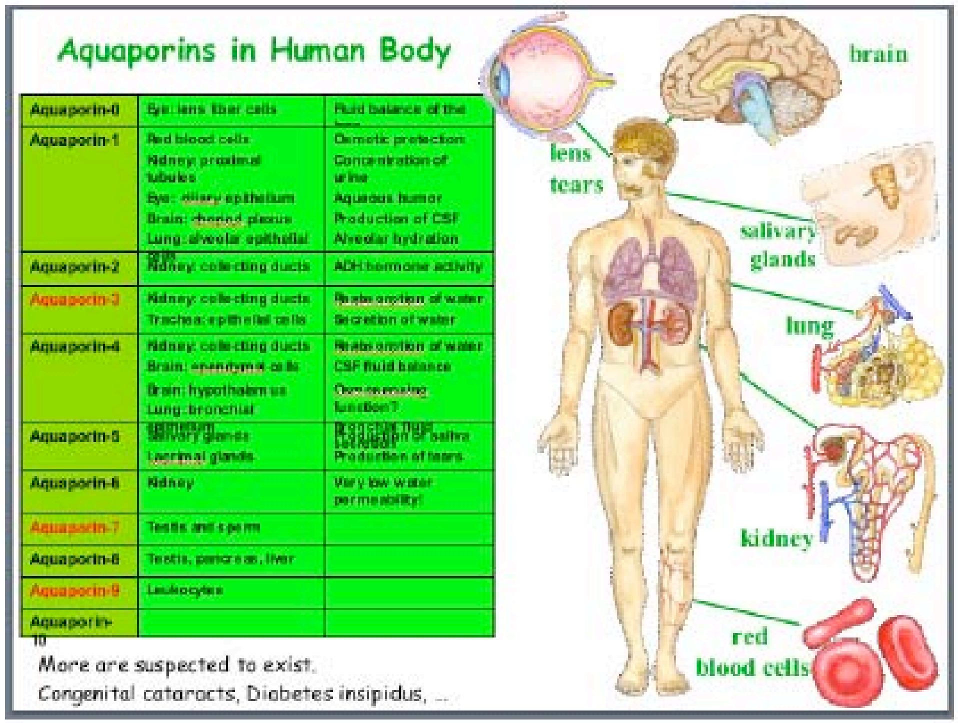
University of Illinois at Urbana-Champaign
NIH Resource for Macromolecular Modeling and Bioinformatics
Beckman Institute

Aquaporins



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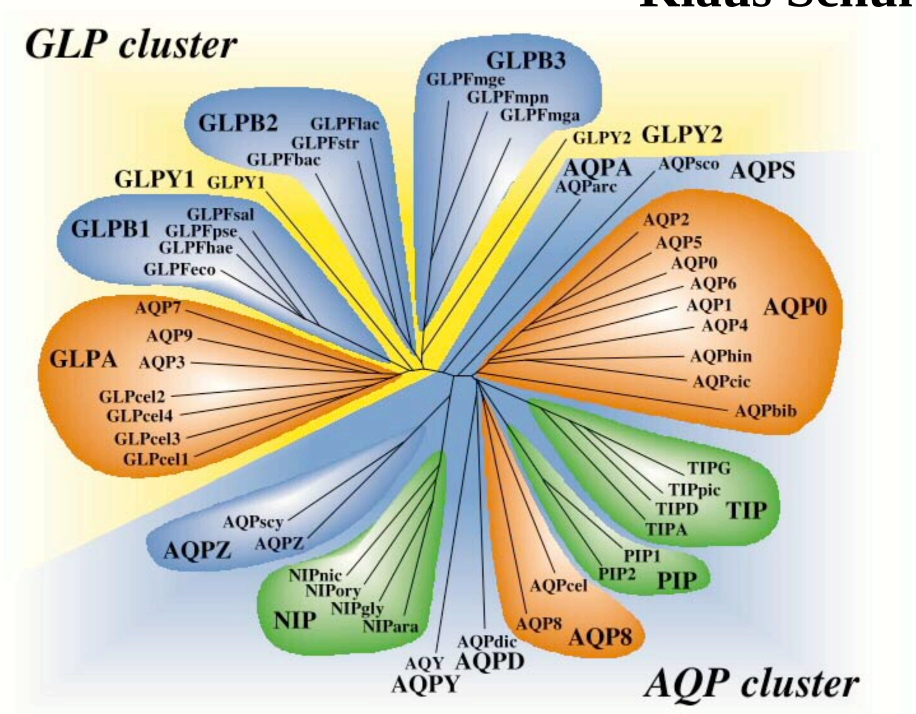
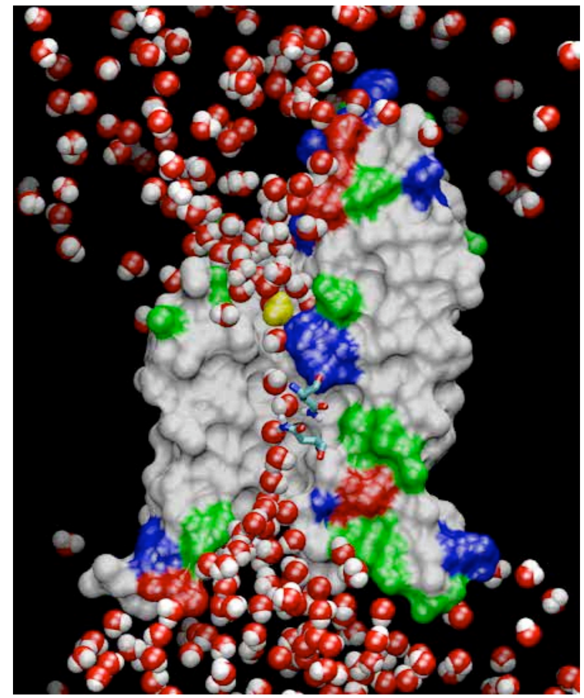
Physical Bioinformatics - A Case Study

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 questions are addressed by means of molecular dynamics simulations using the program NAMD that reveal the physical principles behind water transport and highly selective solute co-transport in aquaporins. Sequence-structure information is viewed again to elucidate tetramer binding and pathologies connected with certain aquaporin mutants. The lecture introduces the concepts behind the programs employed and emphasizes those aspects of the case study that can be applied for investigations of other protein families.

Physical Bioinformatics - A Case Study
Aquaporin Family of Membrane Channels

Klaus Schulten, U. Illinois at Urbana-Champaign





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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....
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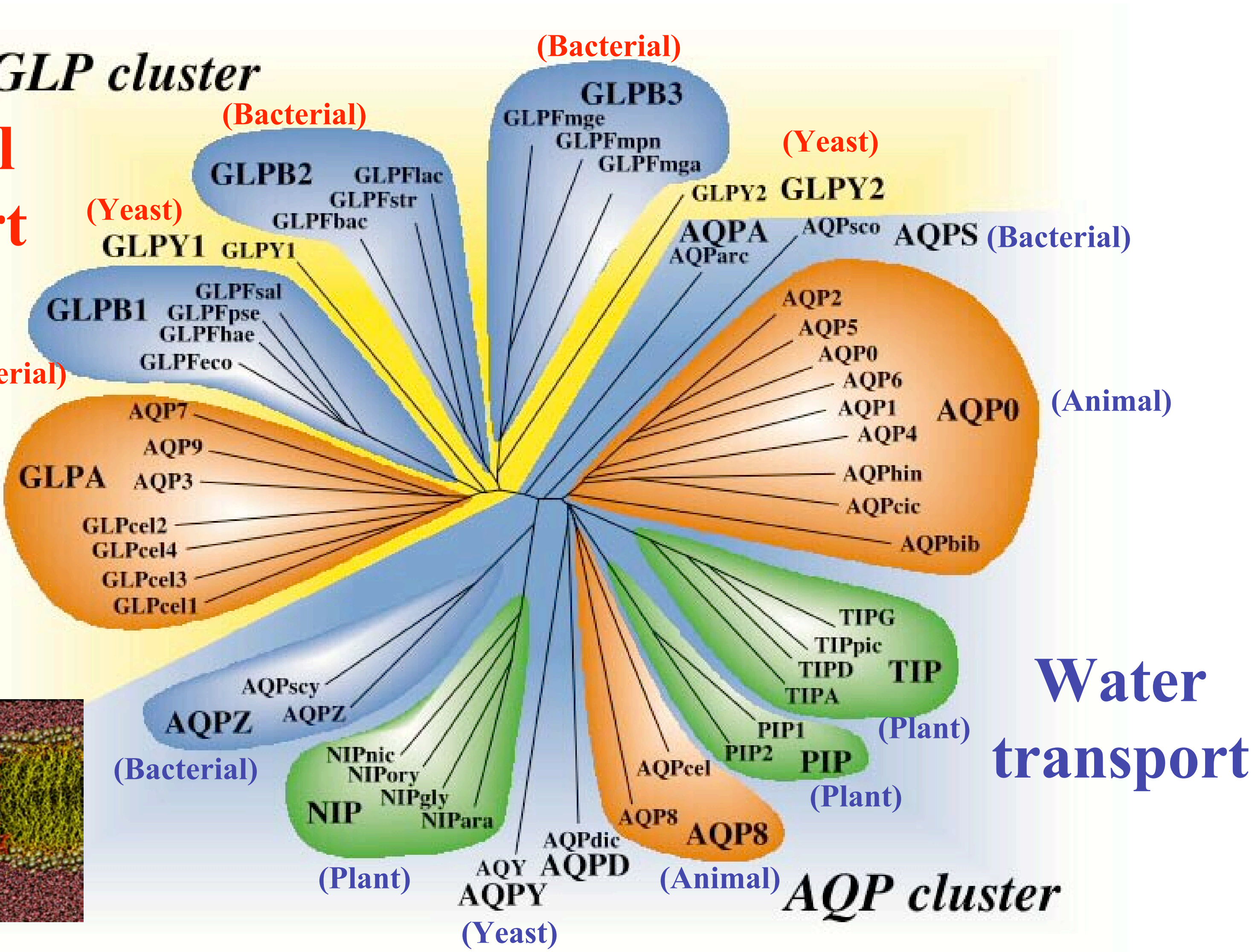
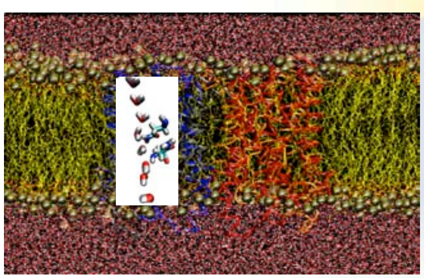
The Aquaporin Superfamily



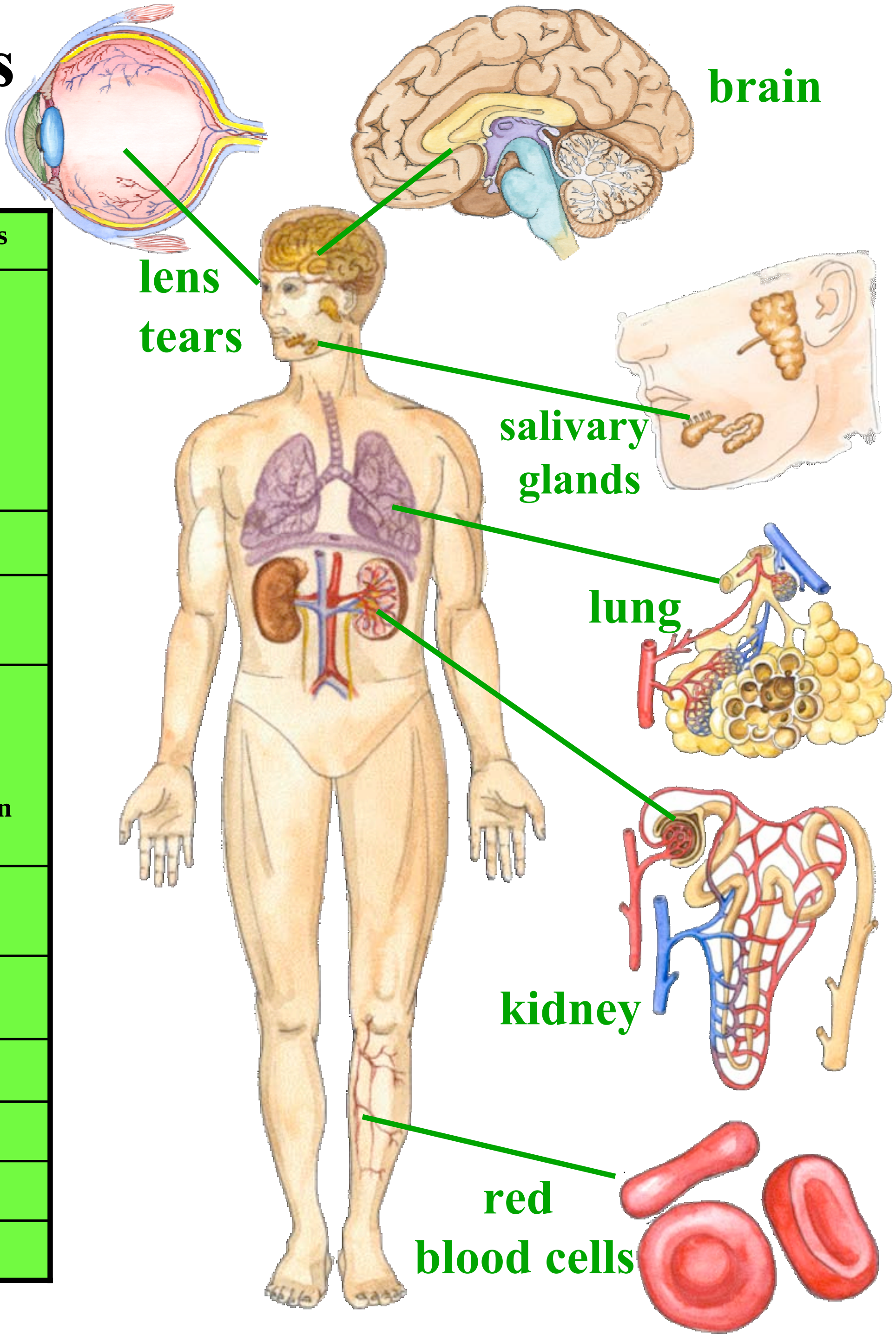


Heymann and Engel *News Physiol. Sci.* **14**, 187 (1999)

Water and Glycerol Channels in the Human Body

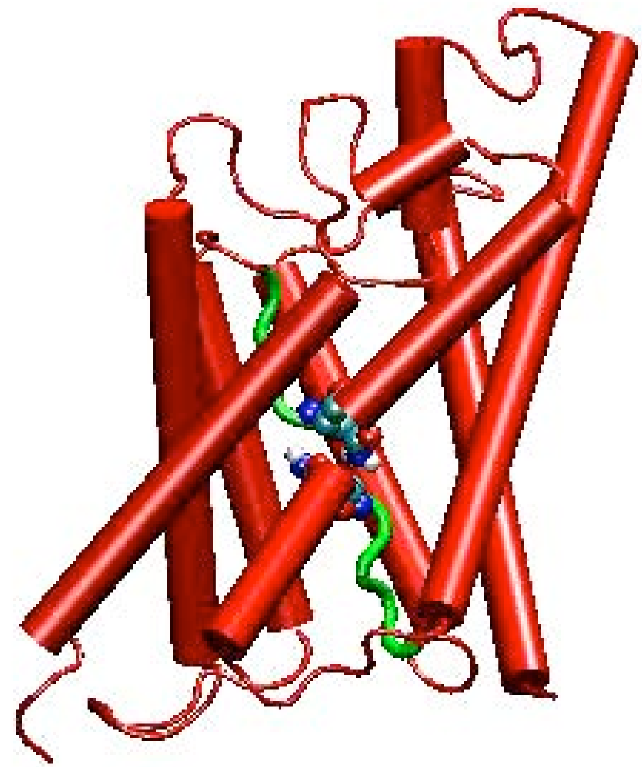
Aquaporin-0	Eye: lens fiber cells	Fluid balance of the lens
Aquaporin-1	Red blood cells Kidney: proximal tubules Eye: ciliary epithelium Brain: choriod plexus Lung: alveolar epithelial cells	Osmotic protection Concentration of urine Aqueous humor Production of CSF Alveolar hydration
Aquaporin-2	Kidney: 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	
Aquaporin-10		

Additional members are suspected to exist.



Functionally Important Features of Aquaporins

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

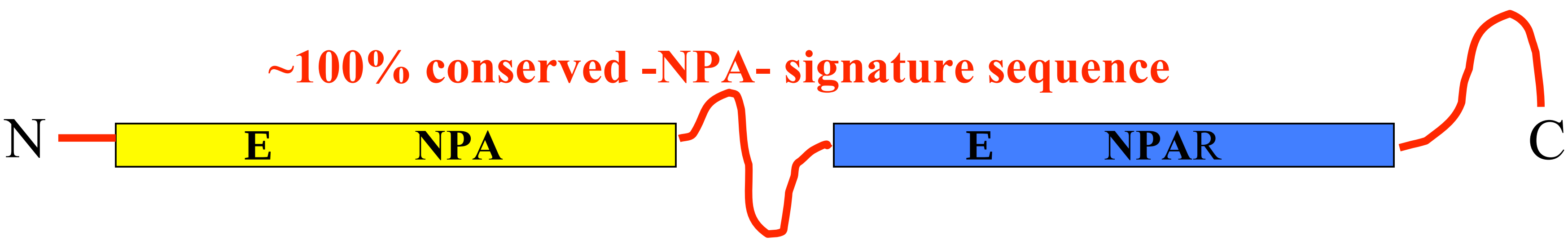


Aquaporins of known structure:

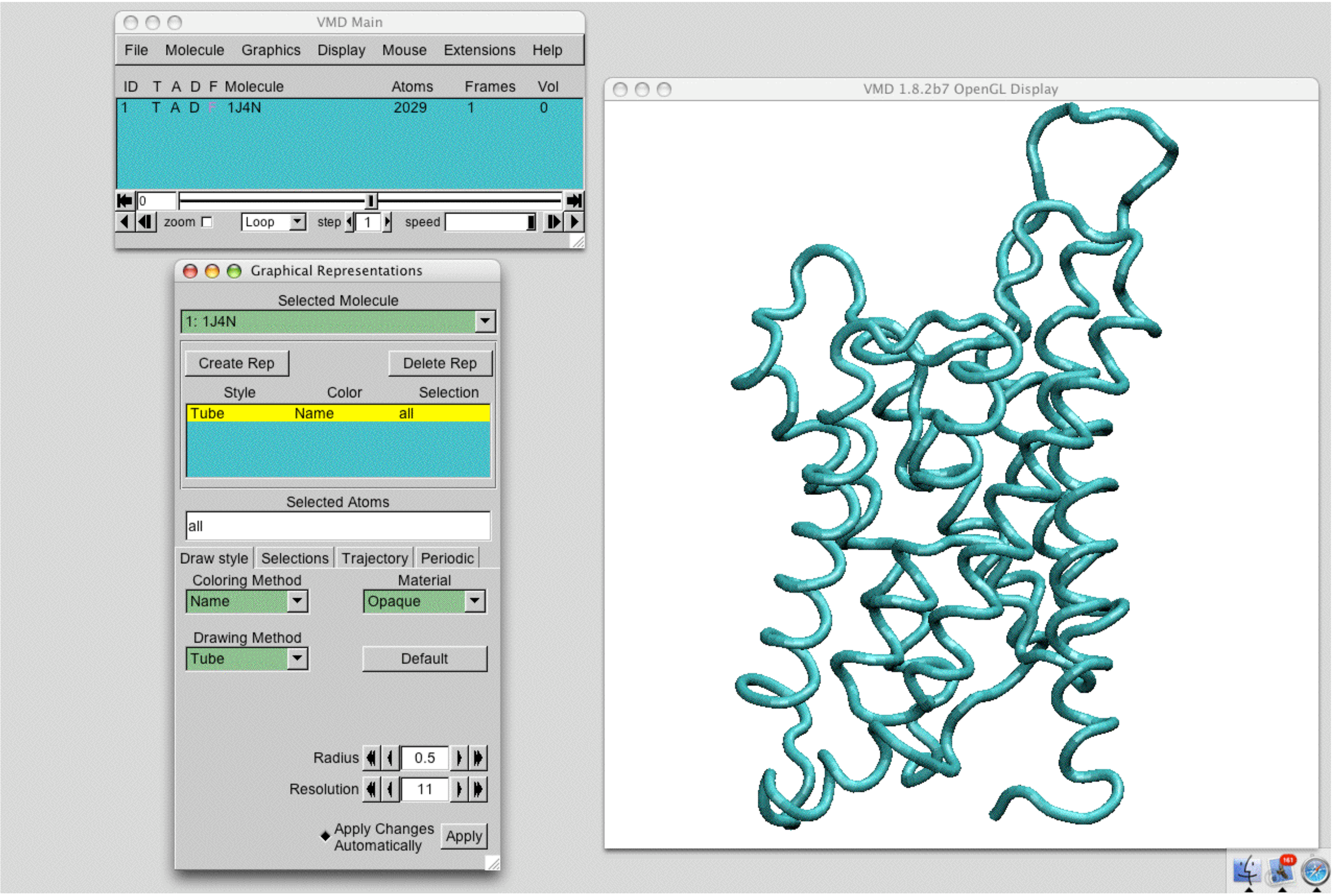
GlpF – E. coli glycerol channel (aquaglyceroporin) – Fu, et al., Science (2000)

AQP1 – Mammalian aquaporin-1 (pure water channel) -Sui et al, Nature (2001)

~100% conserved -NPA- signature sequence

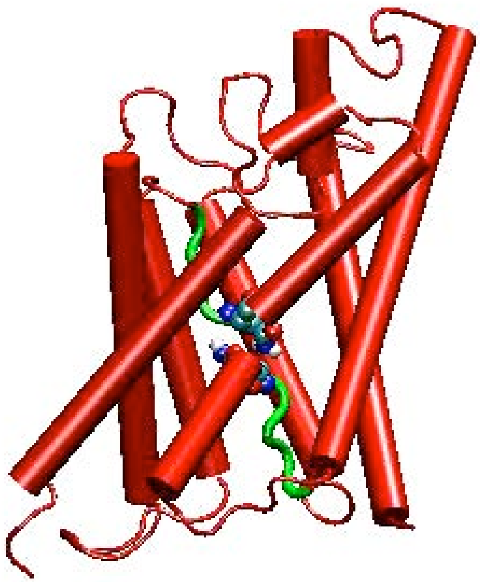


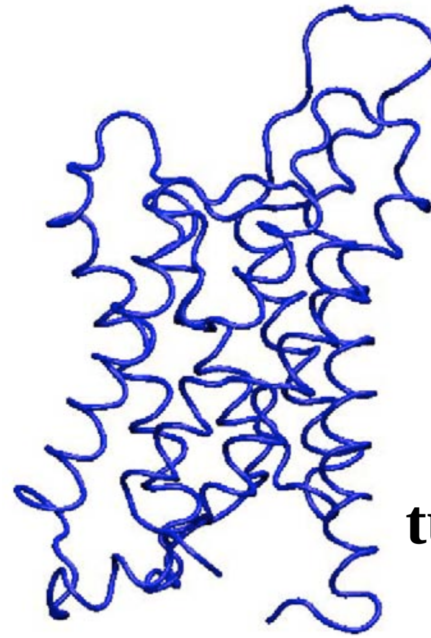
Load Aquaporin 1J4N into VMD



VMD Permits Different Rendering Styles

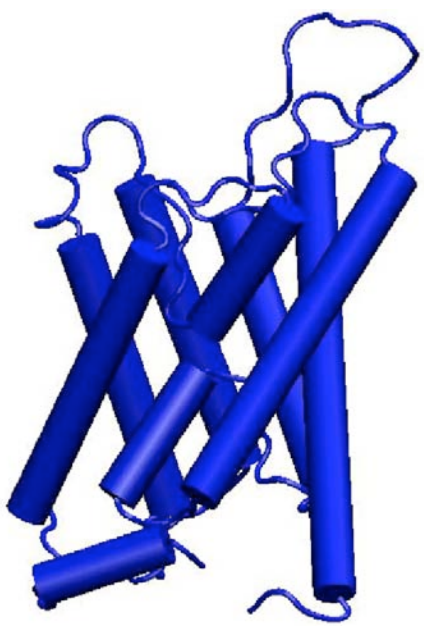
movie

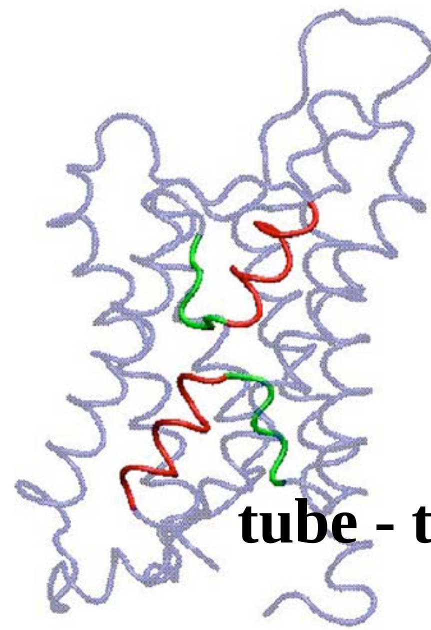




tube

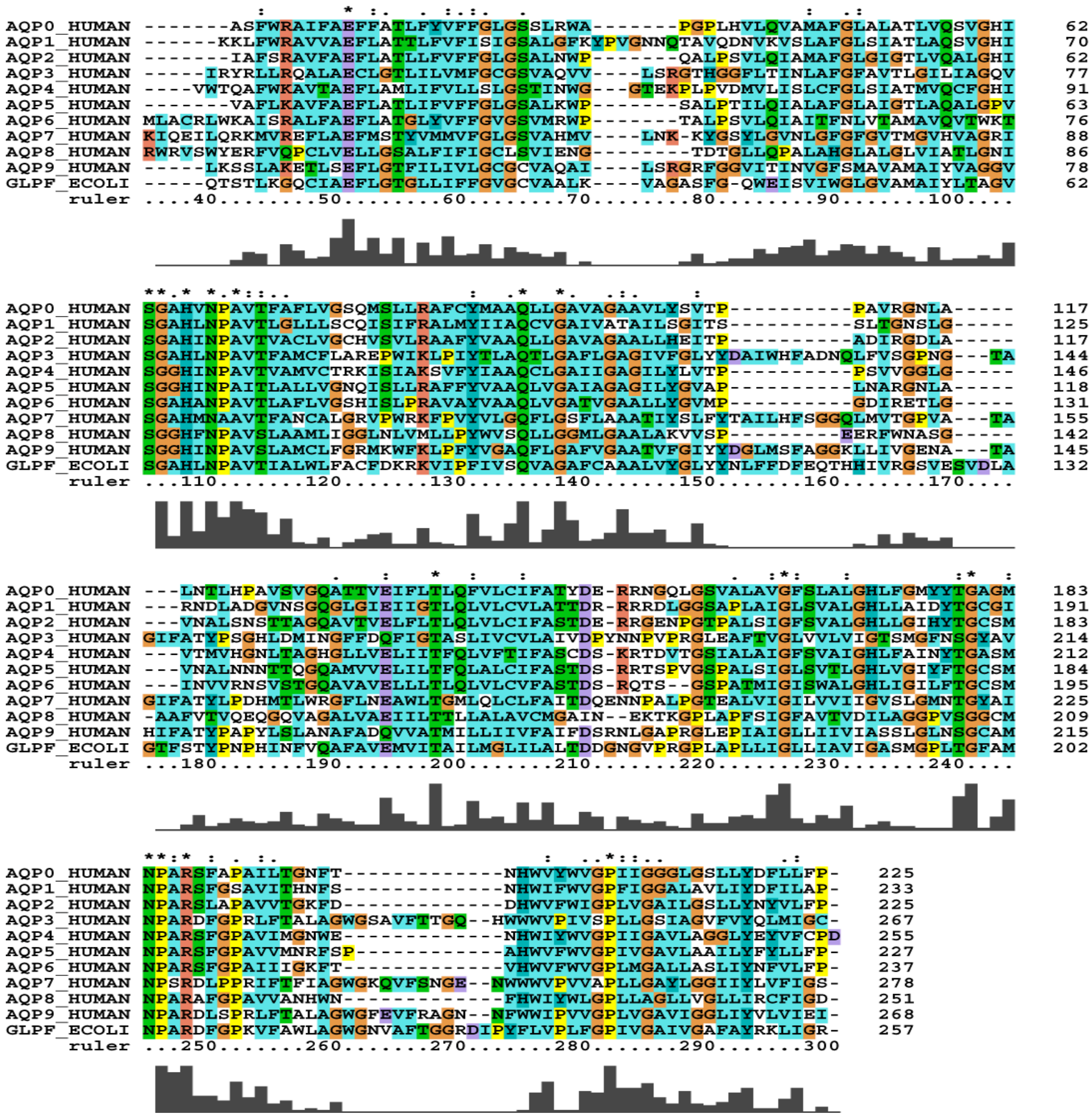
cartoon



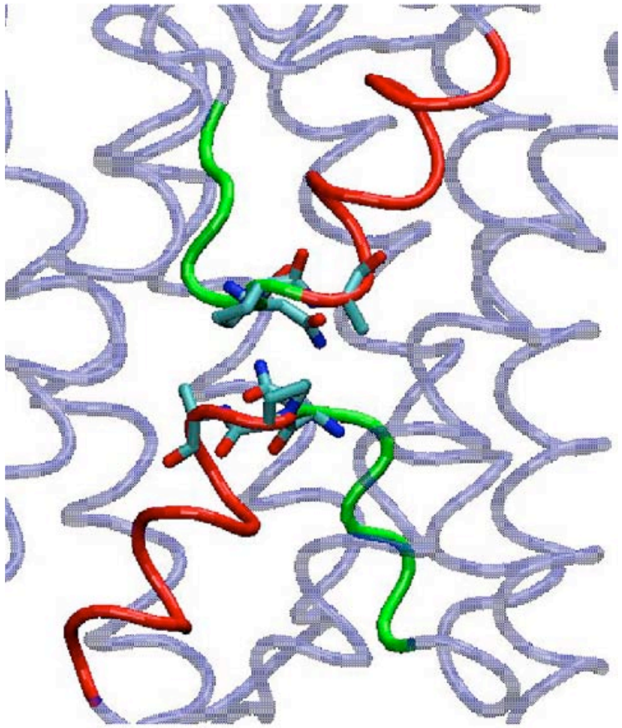


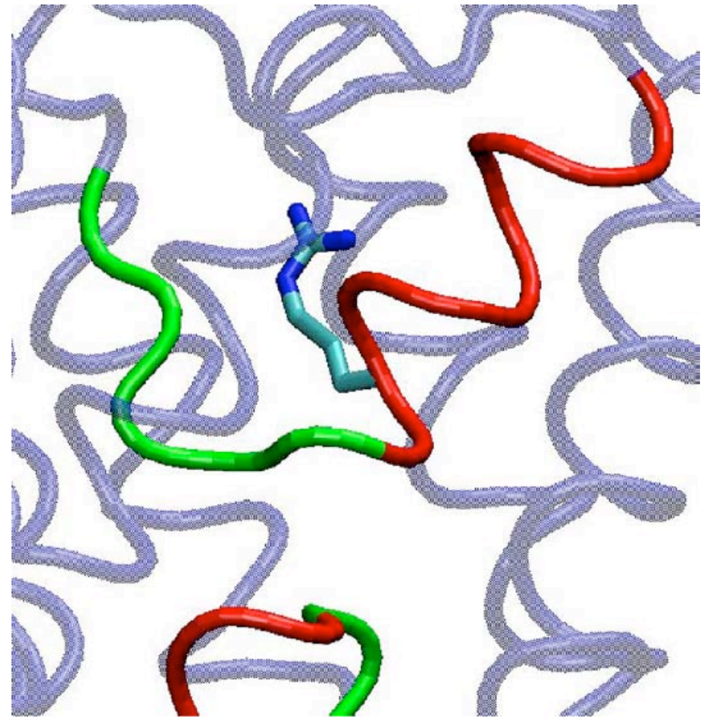
tube - transparent

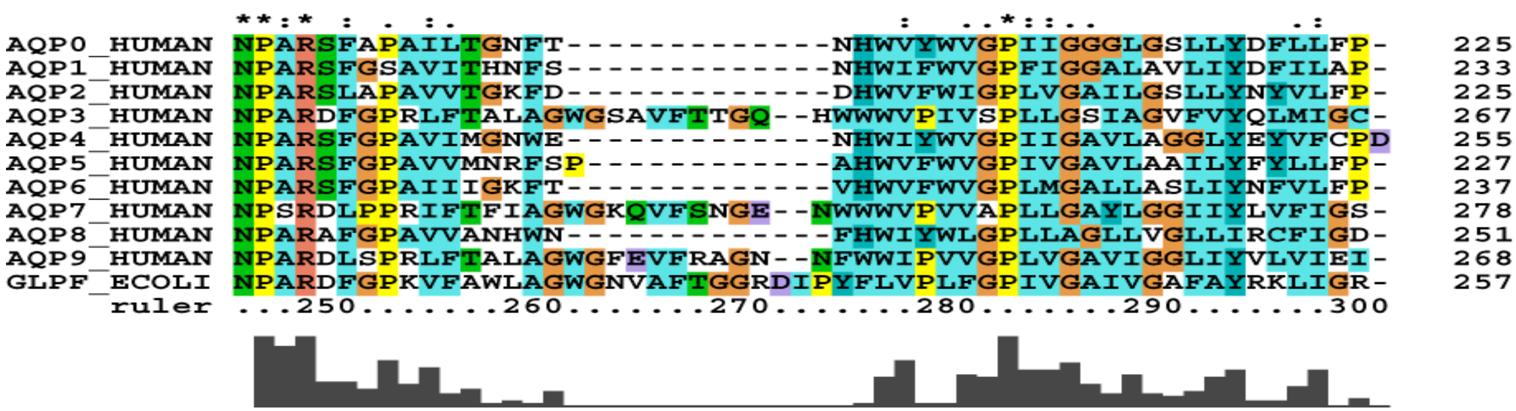
Comparing Sequences of Aquaporins



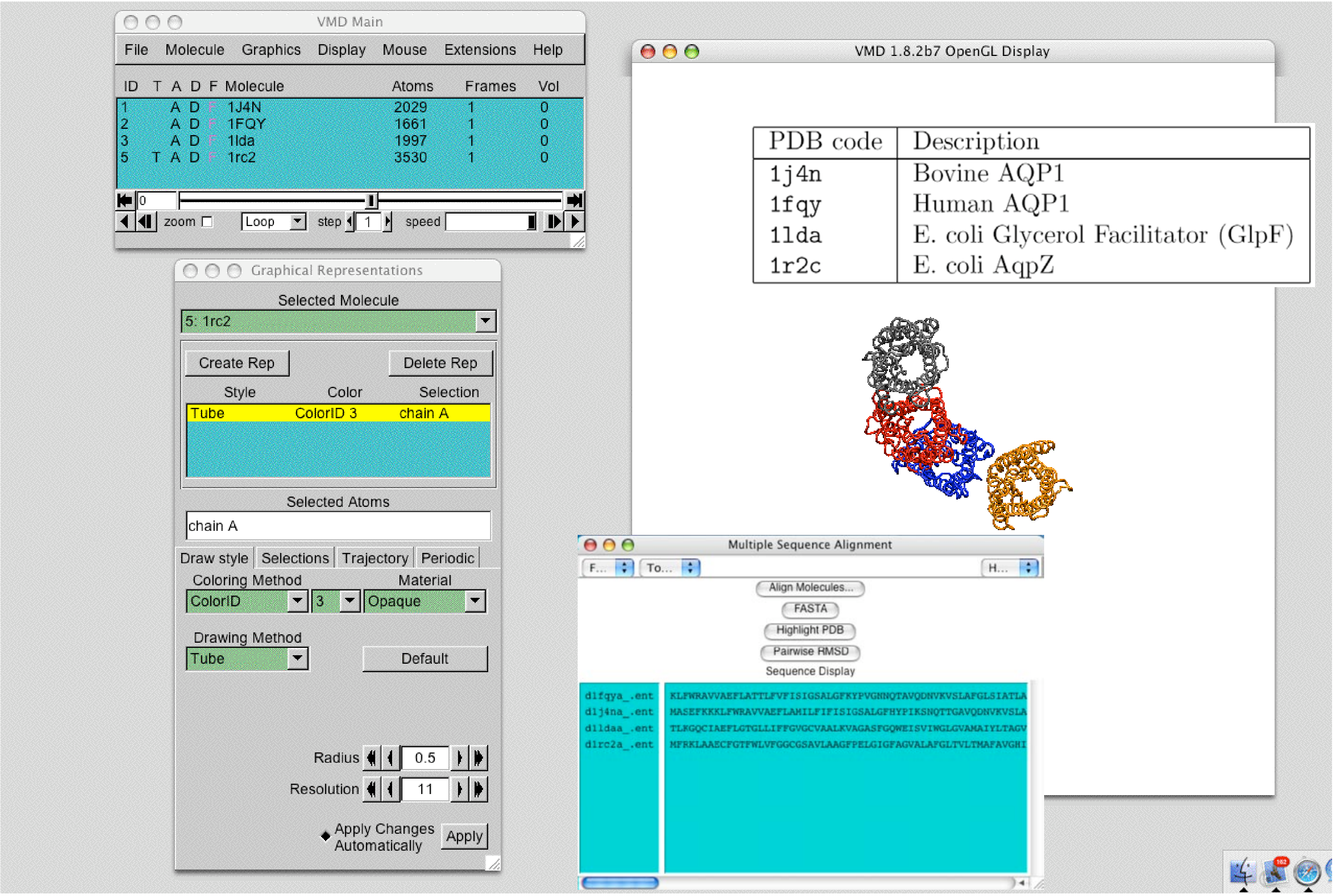
Highlighting Key Conserved Residues



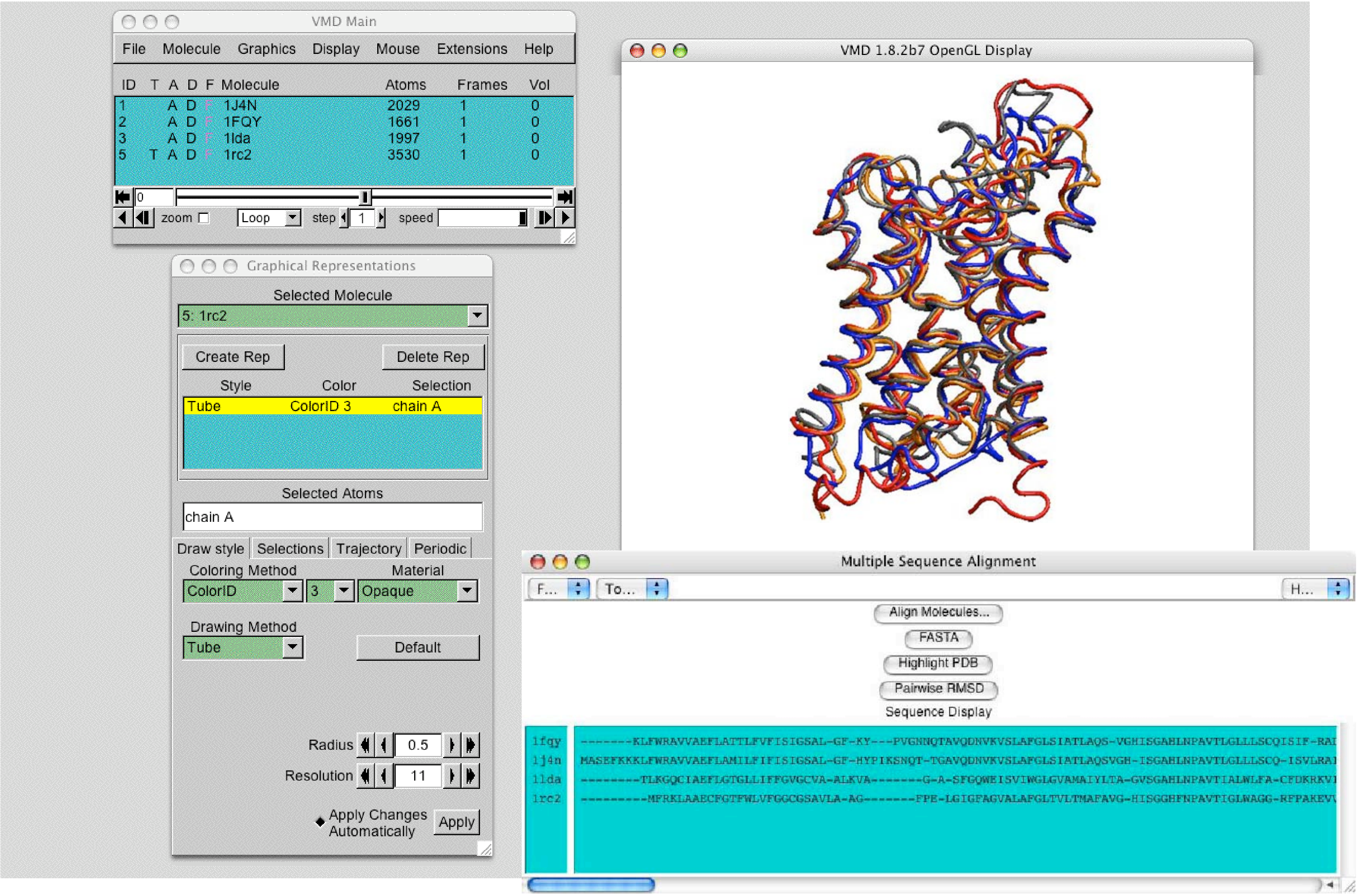




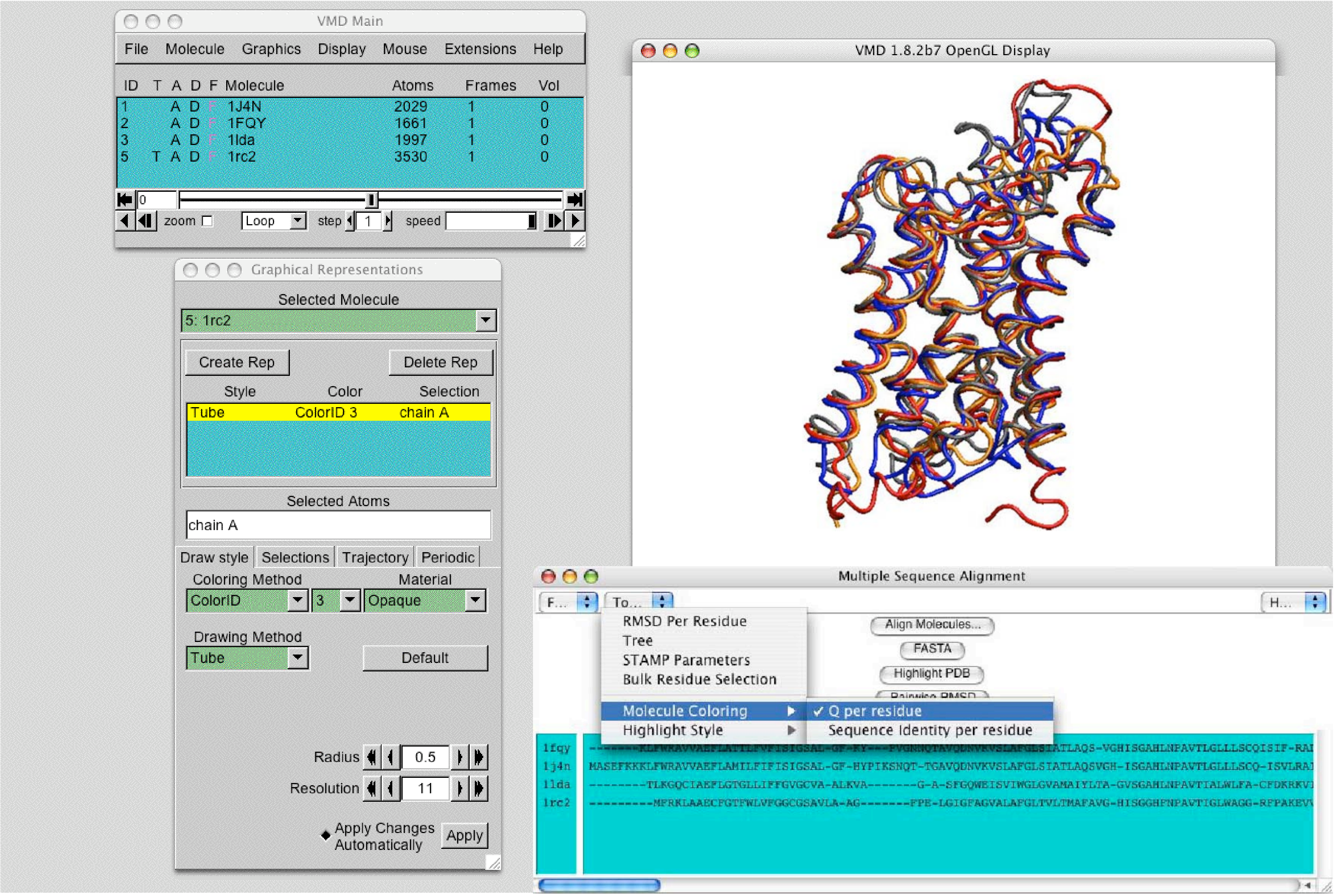
Load Aquaporins 1j4n, 1fqy, 1lda, 1rc2 into VMD



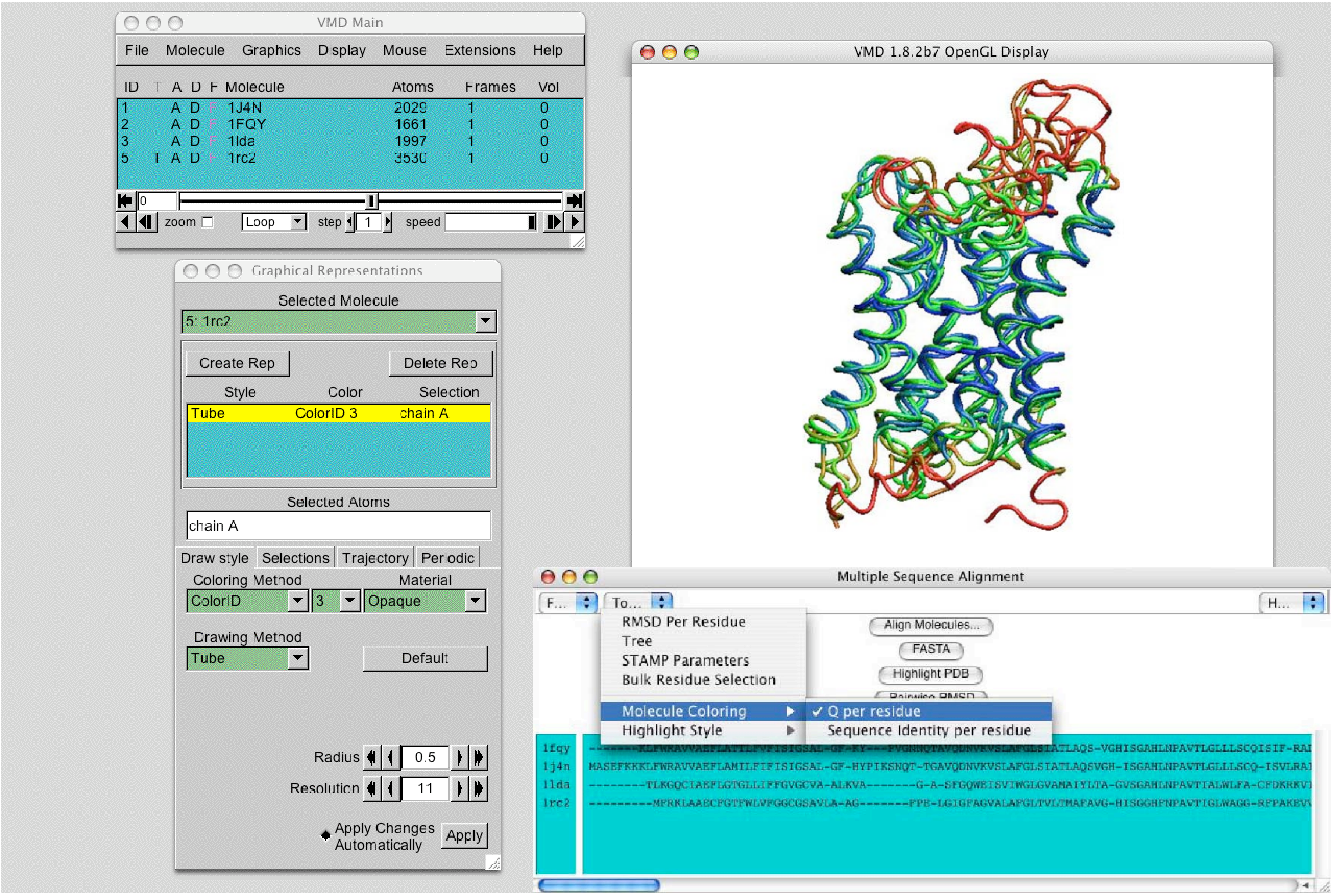
Aligning Structures and Sequences



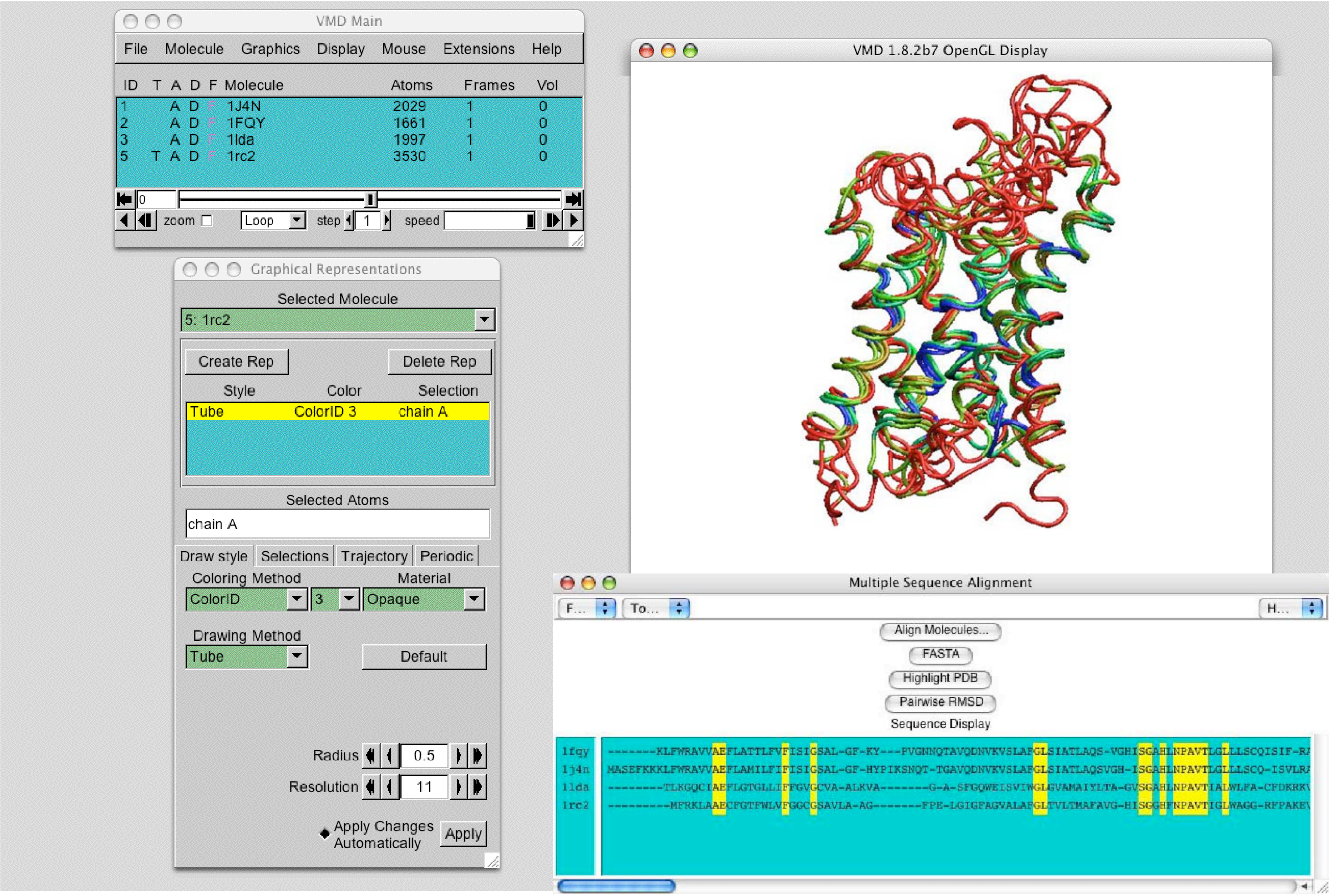
Comparing Structures by Similarity - Q Value



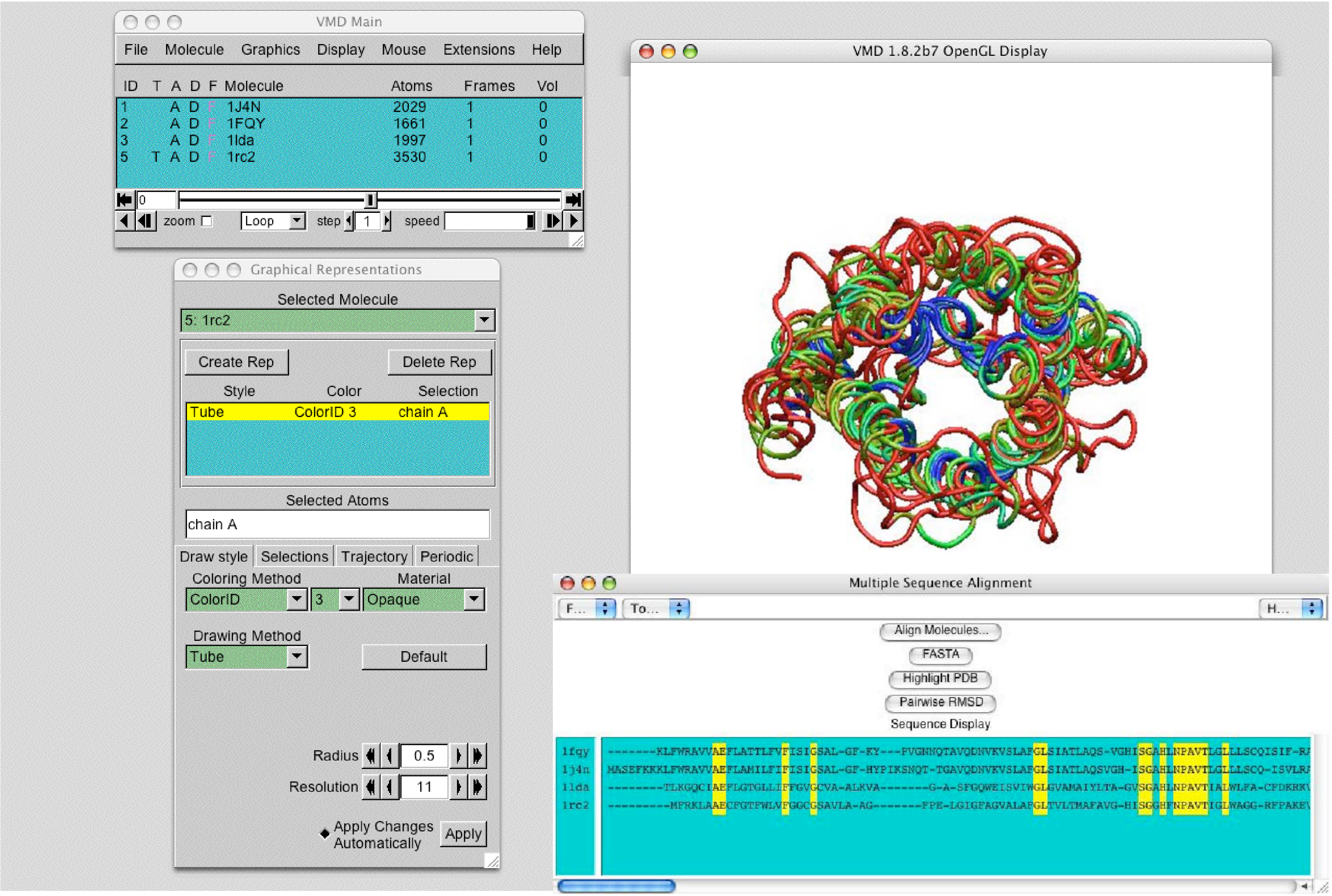
Comparing Structures by Similarity - Q Value



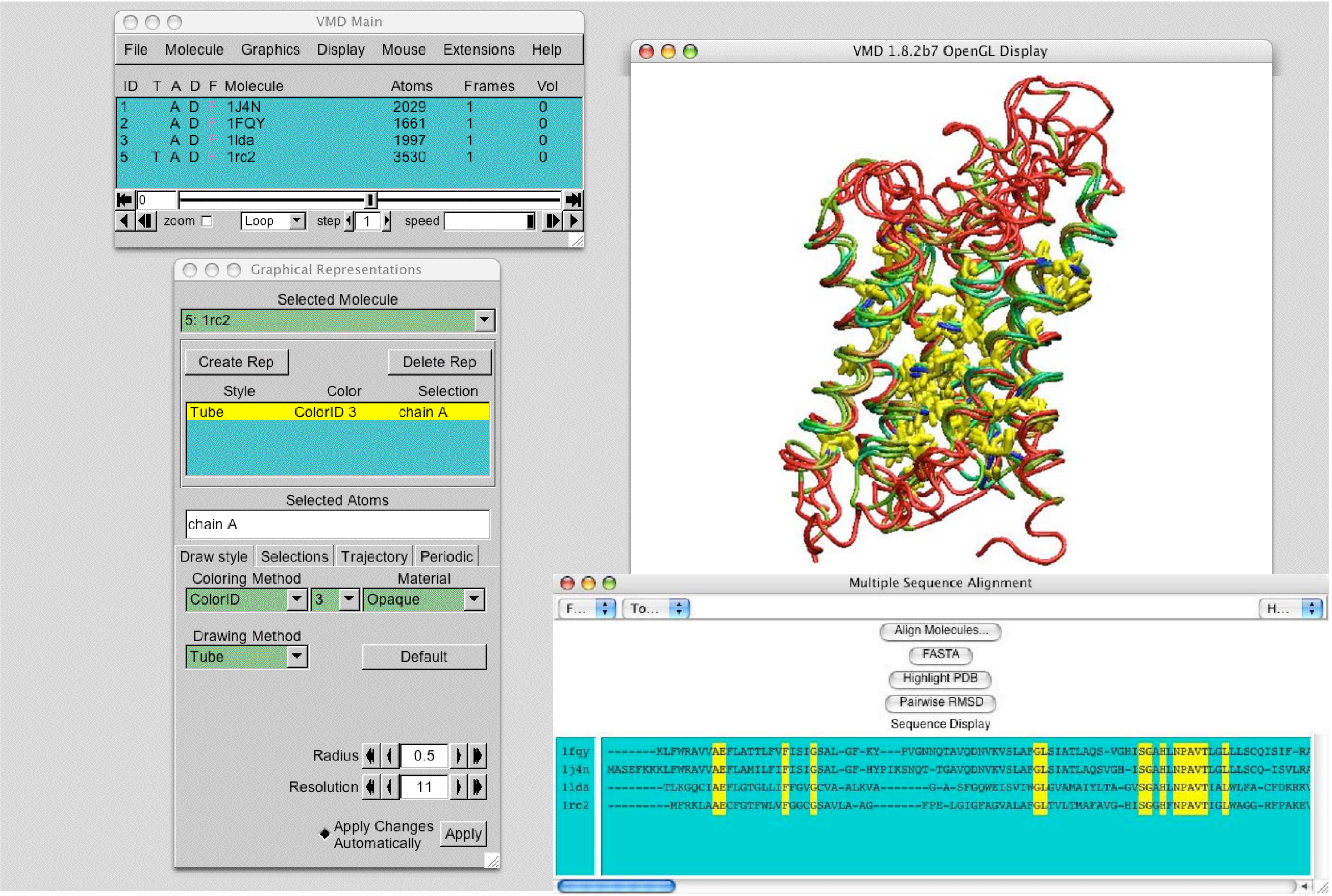
Exhibiting Sequence Identity - Side View



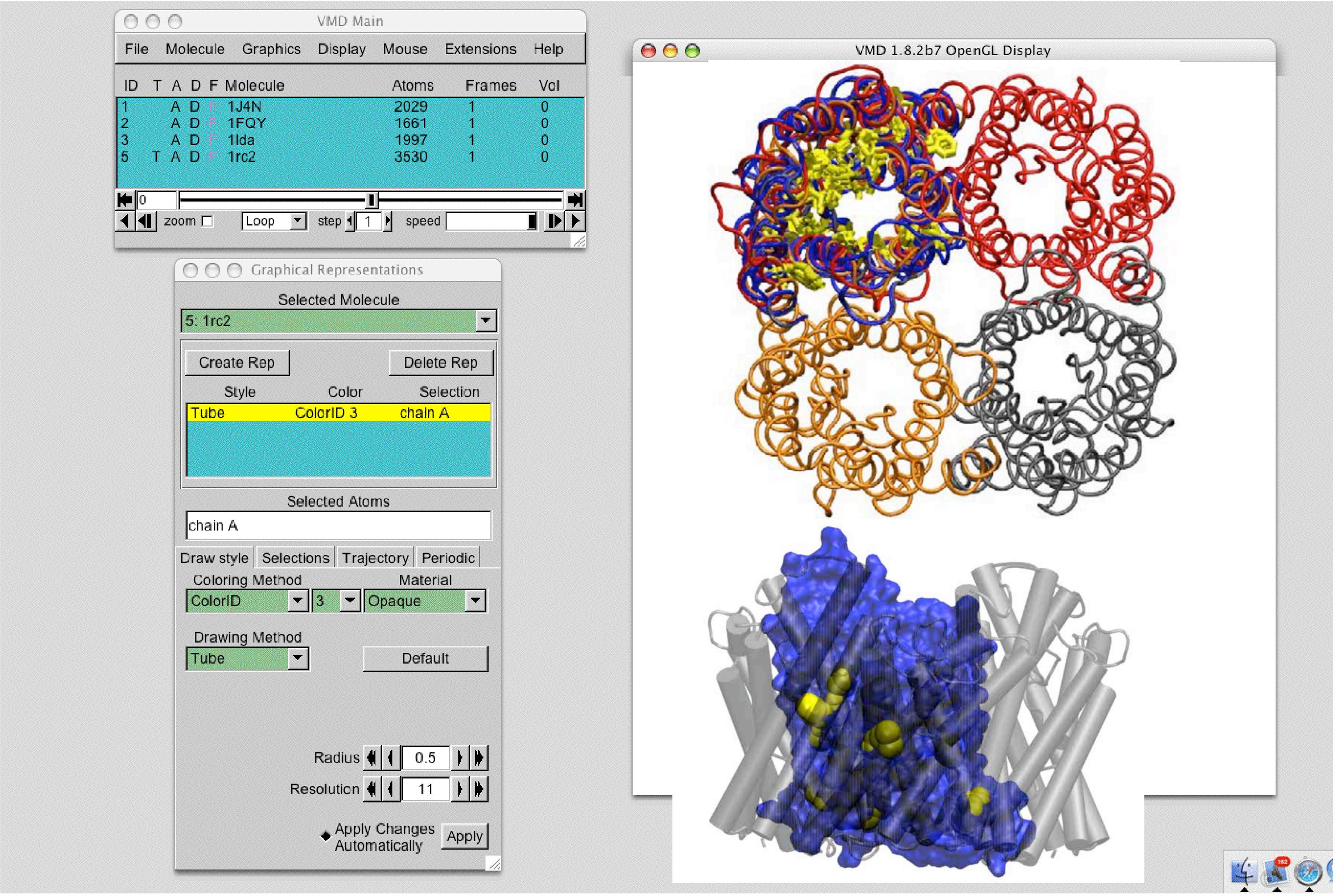
Exhibiting Sequence Identity - Top View



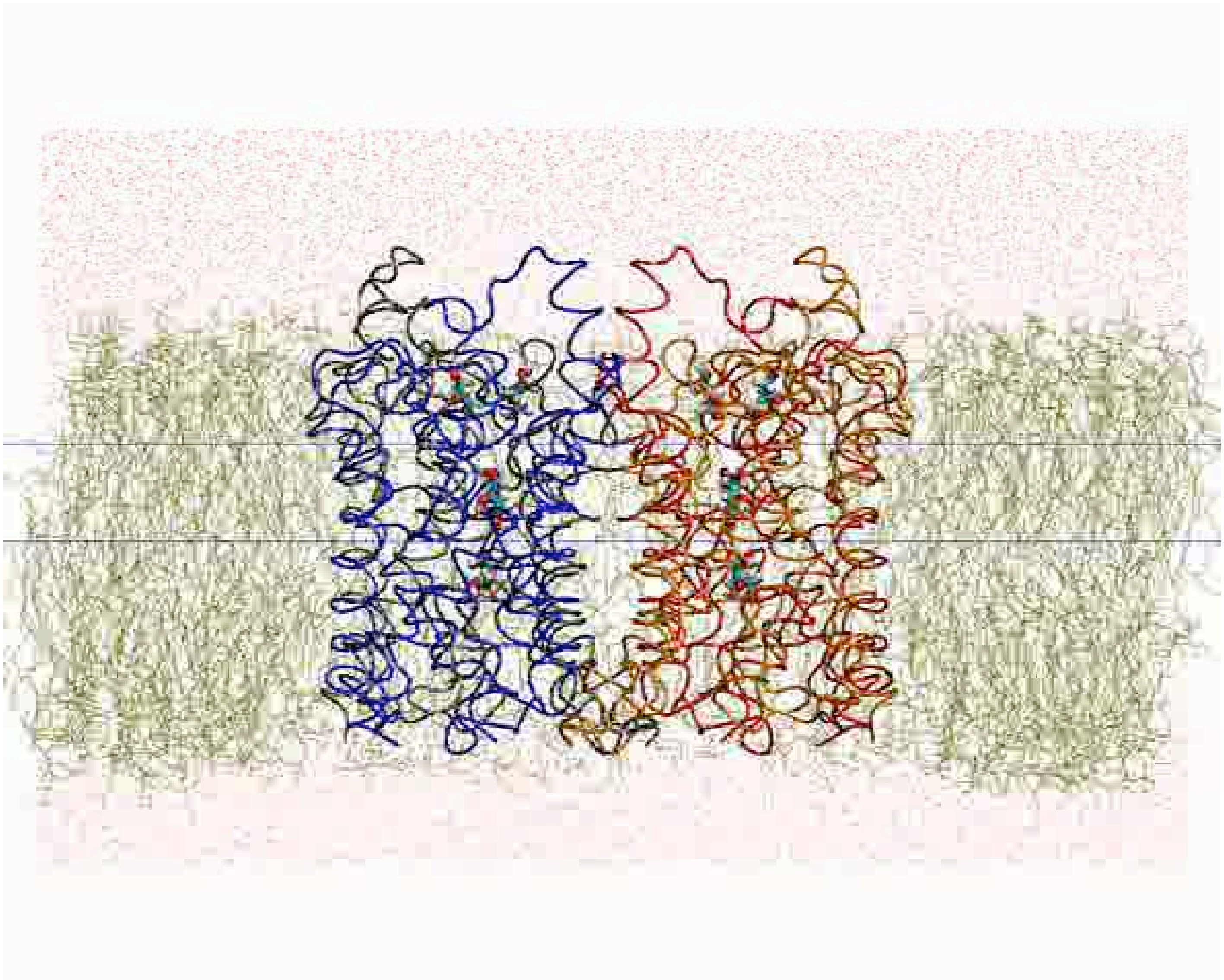
Showing Conserved Residues - Monomer



Showing Conserved Residues - Tetramer

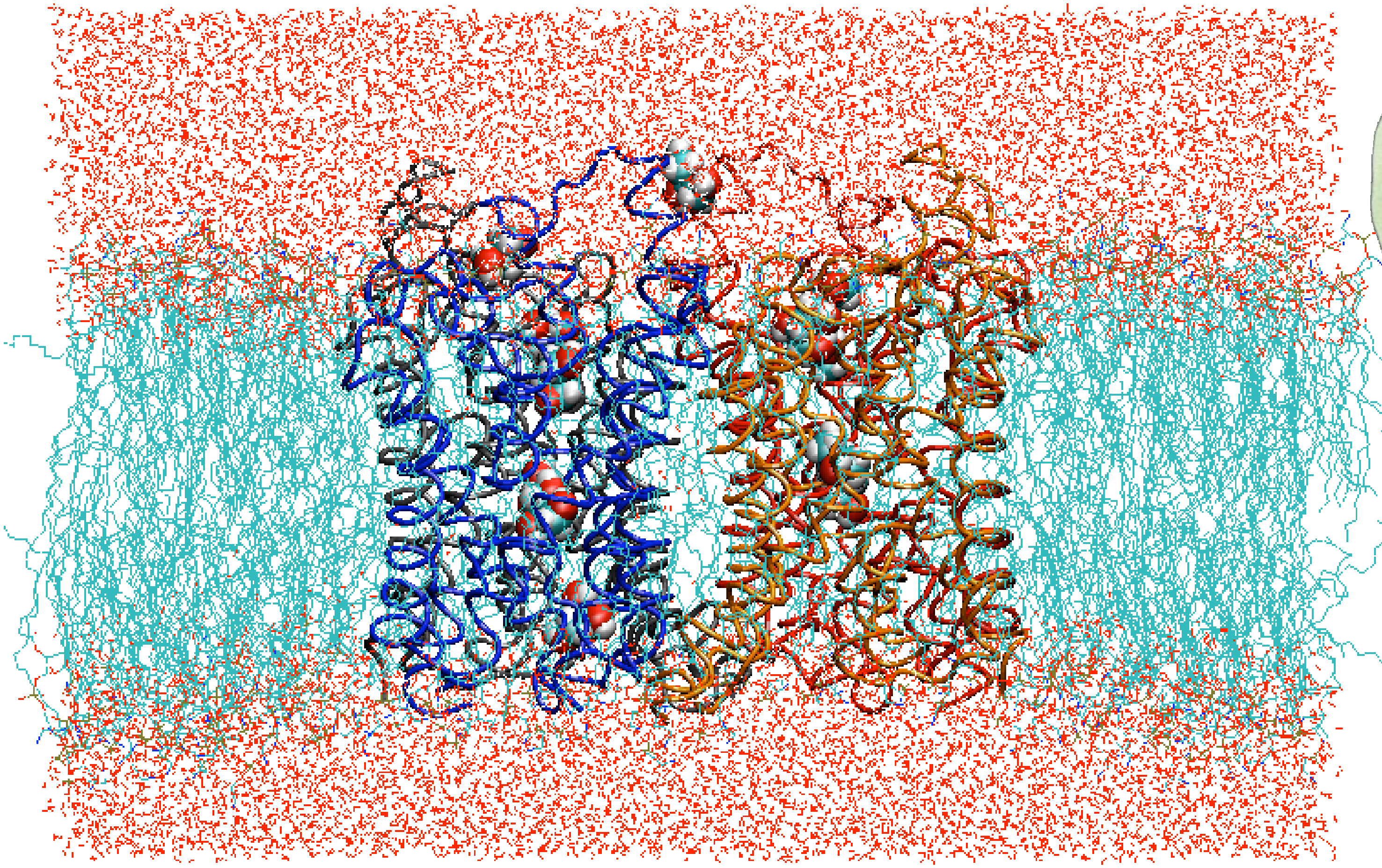


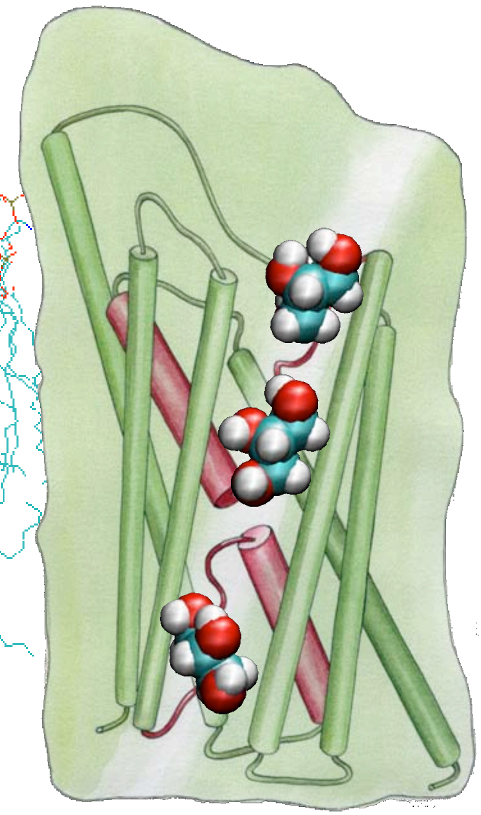
Dynamics of Protein, Lipid, Water System



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

Equilibrated Structure after 1 ns

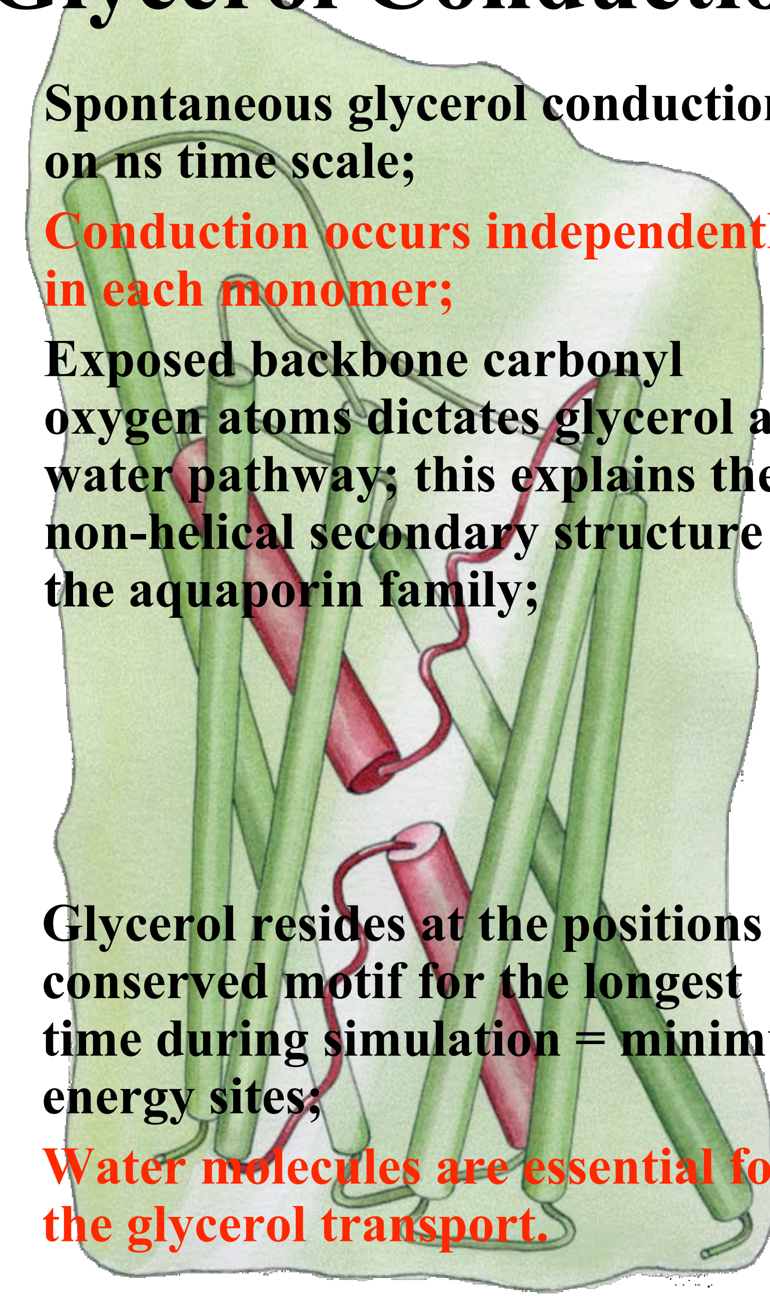




note the curved adjustment between lipids-protein

Morten Jensen, Emad Tajkhorshid

Glycerol Conduction



- Spontaneous glycerol conduction on ns time scale;
- Conduction occurs independently in each monomer;
- Exposed backbone carbonyl oxygen atoms dictates glycerol and water pathway; this explains the non-helical secondary structure in the aquaporin family;
- Glycerol resides at the positions of conserved motif for the longest time during simulation = minimum energy sites;
- Water molecules are essential for the glycerol transport.

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