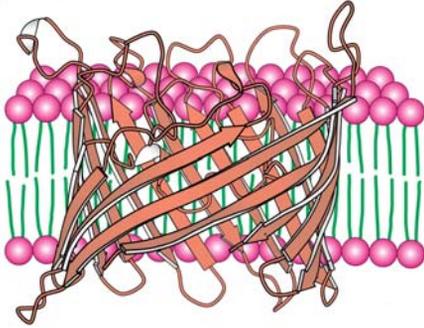


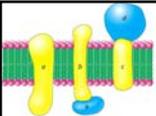
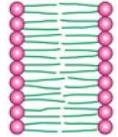
## Principles of Membrane proteins Structure



## Summary of Biological Membranes

- Highly selective permeability barriers
- Amphiphilic organization
- Fluid Mosaic model: liquid and asymmetric
- Fluidity and thickness of membranes are determined by their lipid composition (saturated, longer chains make it less fluid)

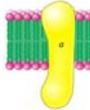
- Hydrophobic core
- Hydrophilic Surfaces



## Membrane Proteins

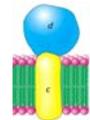
- **Integral - membrane spanning**

Main interaction is **vdW interaction** with the hydrophobic core of the bilayer; therefore, can be isolated from membrane only through membrane disruption, e.g., by detergents; GPCRs, rhodopsins, channels, ...



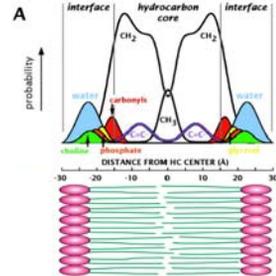
- **Peripheral -**

Do not penetrate the hydrophobic core; main interaction is **electrostatic interaction** with one of the hydrophilic surfaces of the bilayer; usually associated with integral membrane proteins; can be isolated from membrane by strong salt or by changing pH; Cytochrome C

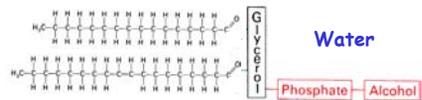


- The bilayer fabric of the membrane has two chemically distinct regions:

Hydrophobic core  
Interfaces

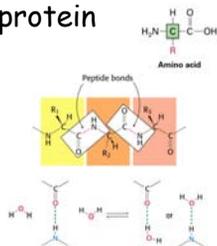


Hydrocarbon



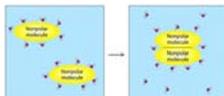
## Major interactions in a protein

- **Polar/Hydrophilic groups:**  
Backbone (C=O and N-H)  
Polar side chains (polar or charged)



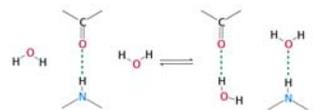
- **Hydrophobic groups:**

Hydrophobic side chains (R)



## A few calculated numbers

water



2.1 kcal/mole

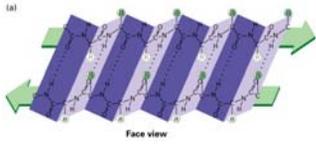
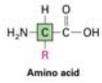
6.4 kcal/mole

alkane

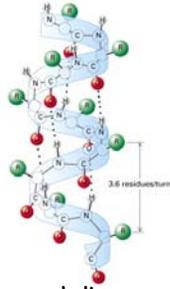
~4.0 kcal/mole

Unfolding of a helix in membrane has an energetic cost of about 4.0 kcal/mole/peptide bond. **Unfolded proteins cannot exist in membrane.** A transmembrane helix of 25 residues forms ~20 hydrogen bonds between its backbone groups.

## Common Folds of Membrane Proteins



$\beta$ -sheet



$\alpha$ -helix

Hydrogen-bond forming groups are satisfied.

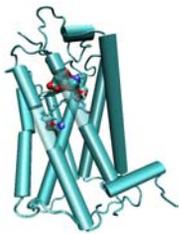
## Common Folds of Membrane Proteins

$\alpha$ -helical - the most common structural fold in membrane proteins: rhodopsins, GPCRs,  $F_0$ -ATPase, Mscl, aquaporins, ion channels, ...

$\beta$ -barrel - Porins: OmpF

## $\alpha$ -helical Membrane Proteins

Rhodopsin



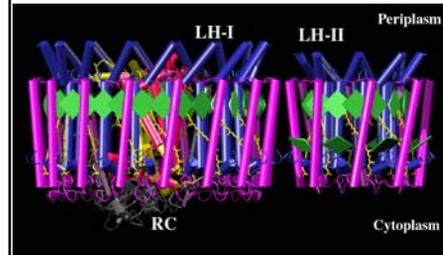
Bacteriorhodopsin



Check G1pF in VMD

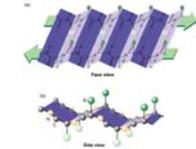
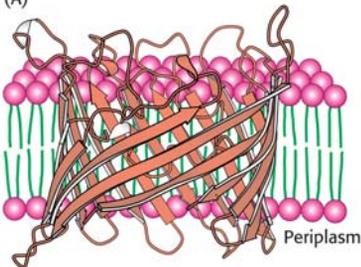
## $\alpha$ -helical Membrane Proteins

Bacterial Photosynthetic Membrane



## $\beta$ -barrel Membrane Proteins

(A)

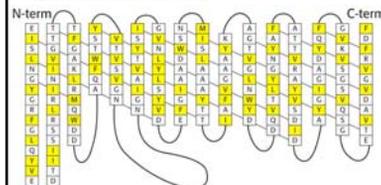
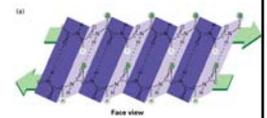


(B)



~18  $\beta$ -strands - found in outer membranes of  $G^-$  bacteria and mitochondria  
Diameter = minimum 7.0 Å

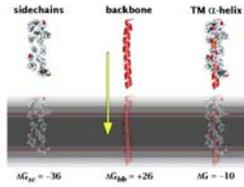
## $\beta$ -barrel Membrane Proteins



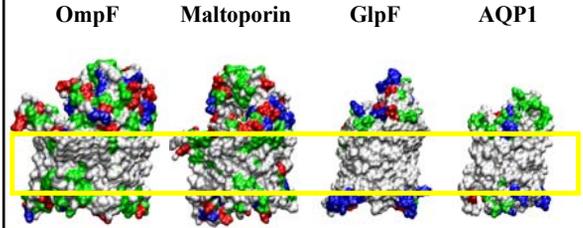
Check OmpF in VMD

## Role of side chains

- Non-polar residues interact with the hydrophobic core of the membrane
- Polar residues interact with head groups and aqueous solution.

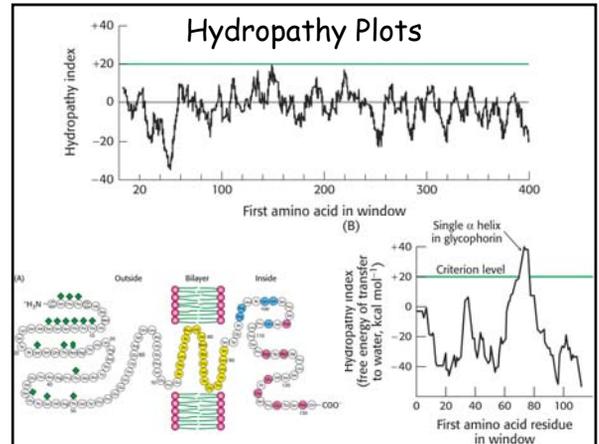


## Protein-Membrane Interaction



Prediction of transmembrane regions?

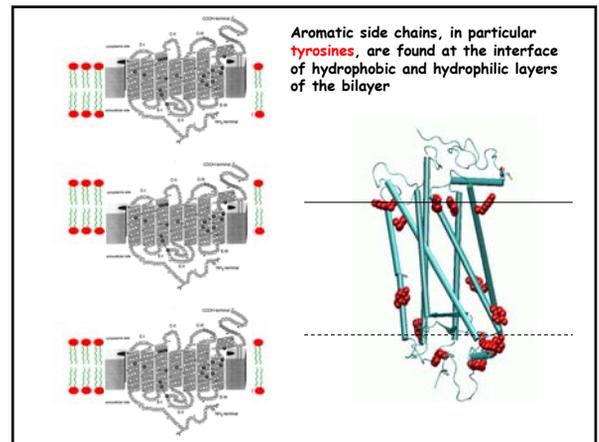
Amino acid residue	Transfer free energy kcal mol <sup>-1</sup> (kJ mol <sup>-1</sup> )
Phe	3.7 (15.5)
Met	3.4 (14.3)
Ile	3.1 (13.0)
Leu	2.8 (11.8)
Val	2.6 (10.9)
Cys	2.0 (8.4)
Trp	1.9 (8.0)
Ala	1.6 (6.7)
Thr	1.2 (5.0)
Gly	1.0 (4.2)
Ser	0.6 (2.5)
Pro	-0.2 (-0.8)
Tyr	-0.7 (-2.9)
His	-3.0 (-12.6)
Gln	-4.1 (-17.2)
Asn	-4.8 (-20.2)
Glu	-8.2 (-34.4)
Lys	-8.8 (-37.0)
Asp	-9.2 (-38.6)
Arg	-12.3 (-51.7)



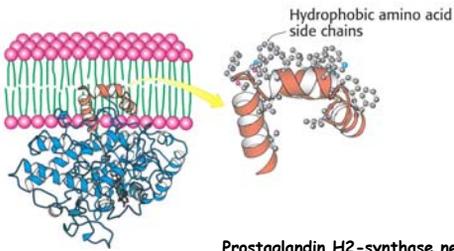
## Prediction of transmembrane regions of membrane proteins by hydropathy plots ...

Failures:

- False positive: hydrophobic parts of globular proteins
- beta-barrel structures
- helices including a highly hydrophilic surface
- Assembly of transmembrane helices cannot be predicted

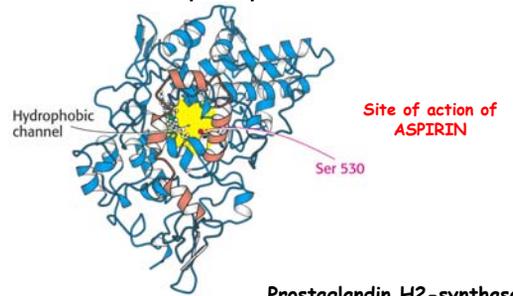


## Membrane-anchored proteins



Prostaglandin H2-synthase needs to be close to membrane, since its substrate, arachidonic acid, is a fatty acid in the membrane and cannot be found in cytoplasm.

## Reverse bundles: Hydrophobic inside, hydrophilic outside

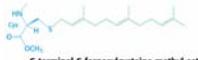


Prostaglandin H2-synthase

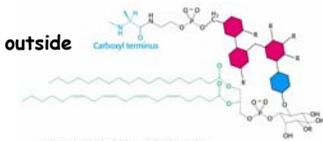
## Covalent Tethering of Membrane Proteins to Membranes



S-Palmitoylcysteine



C-terminal S-farnesylcysteine methyl ester



Glycosyl phosphatidylinositol (GPI) anchor

Critical for protein function: **LOCATION**  
Often found in proteins involved in cell signaling

