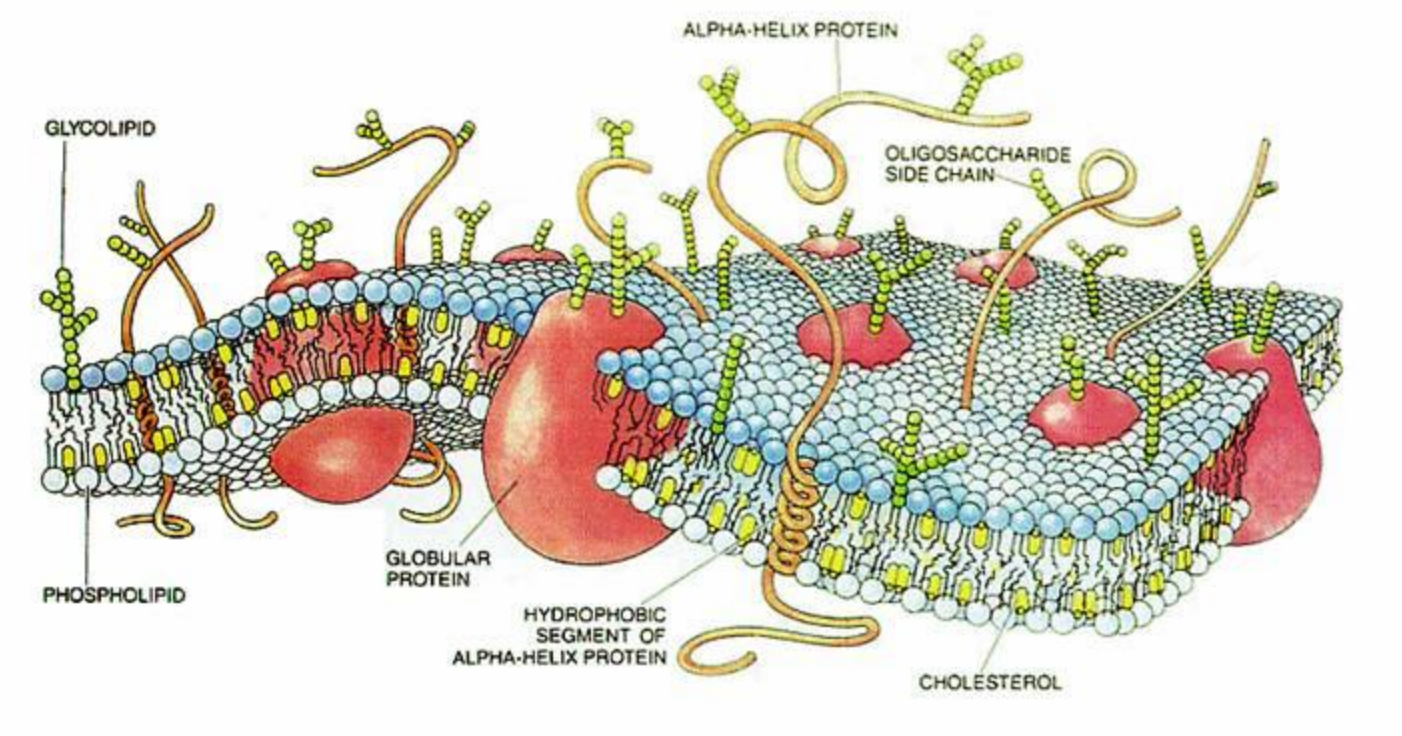
MEMBRANE PROTEIN

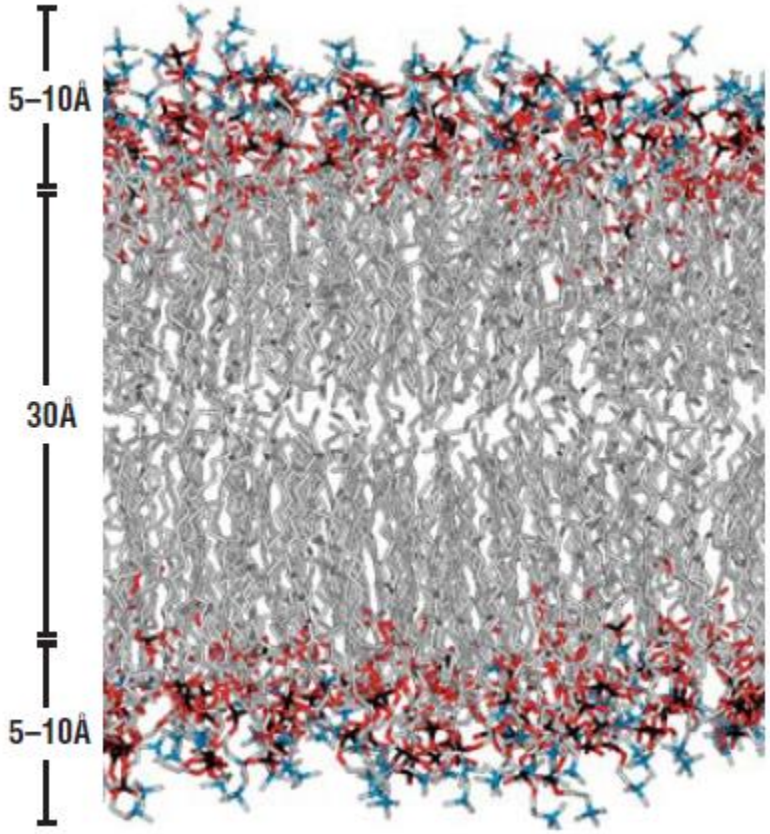
Dr. Zhiyi Wei
SUSTC

Membrane embedded proteins



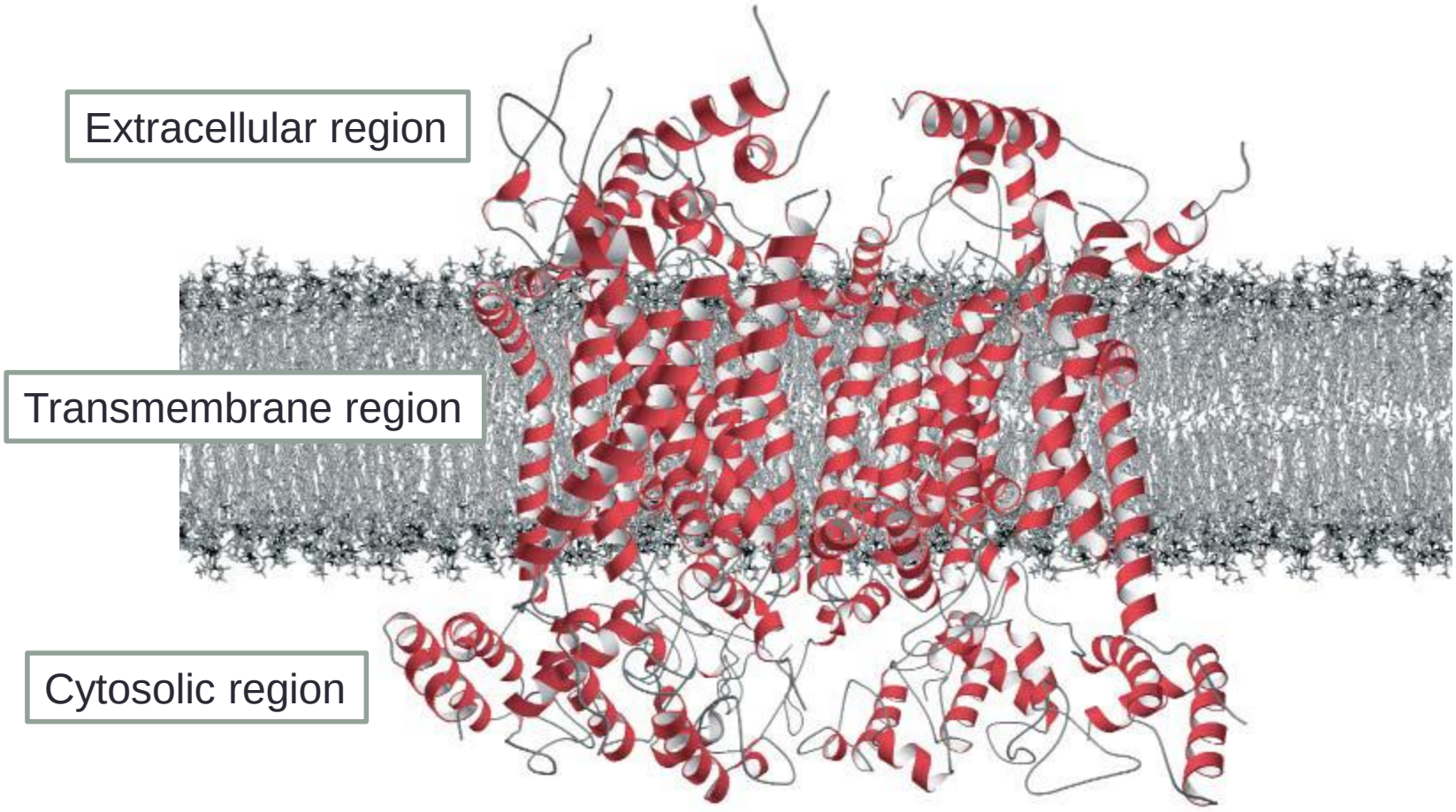
Bretcher, Scientific American, 1985

The unique properties of membrane



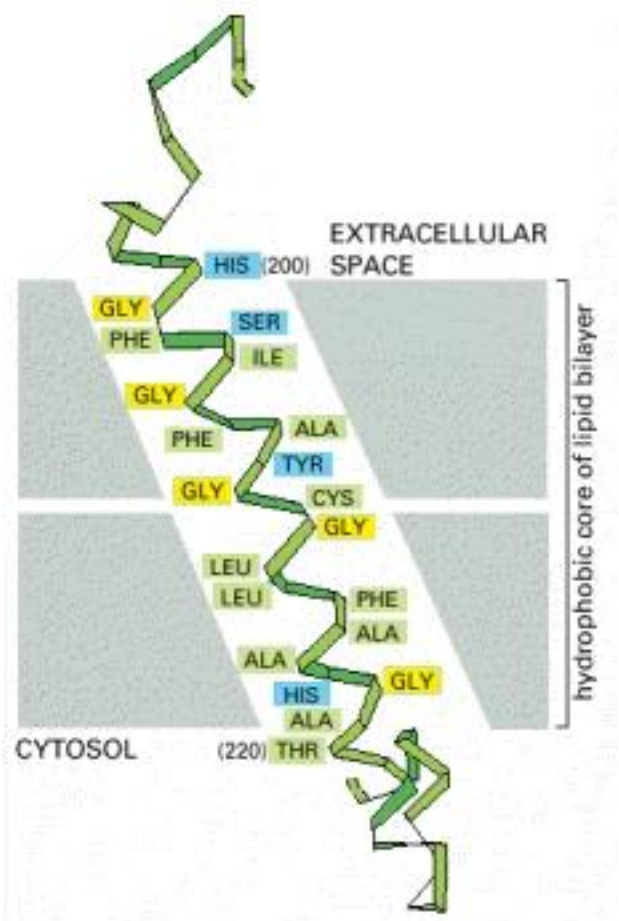
- Lipid bilayer
- Charged-hydrophobic-charged Sandwich
- Hydrophobic environment for protein folding
  - The same secondary structure elements as those for water-soluble proteins
  - Favor for α-helices and β-sheets
    - Stronger hydrogen bonds
    - A single helix can exist stably in a membrane

Membrane protein folding



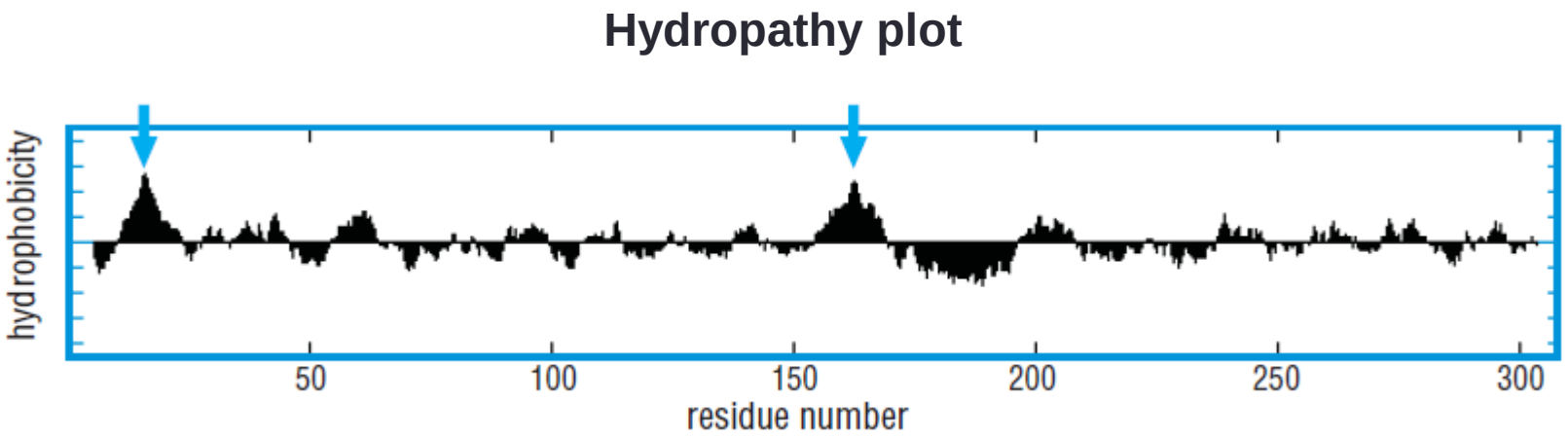
The cytochrome bc1 complex (PDB 1BGY)

Transmembrane helix



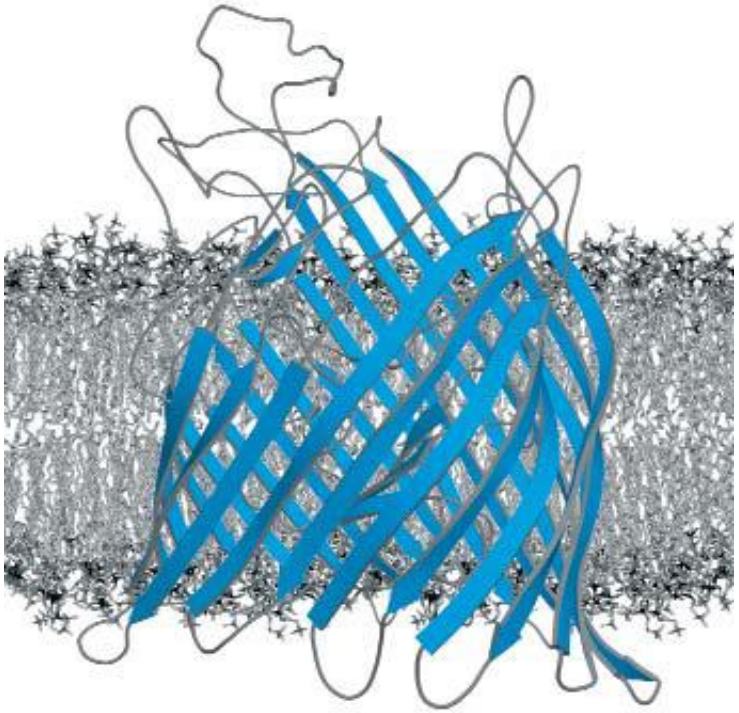
Prediction of transmembrane helix

- Continuous hydrophobic residues
  - 1.5 Å translation per residue in an α-helix
  - ~20 residues



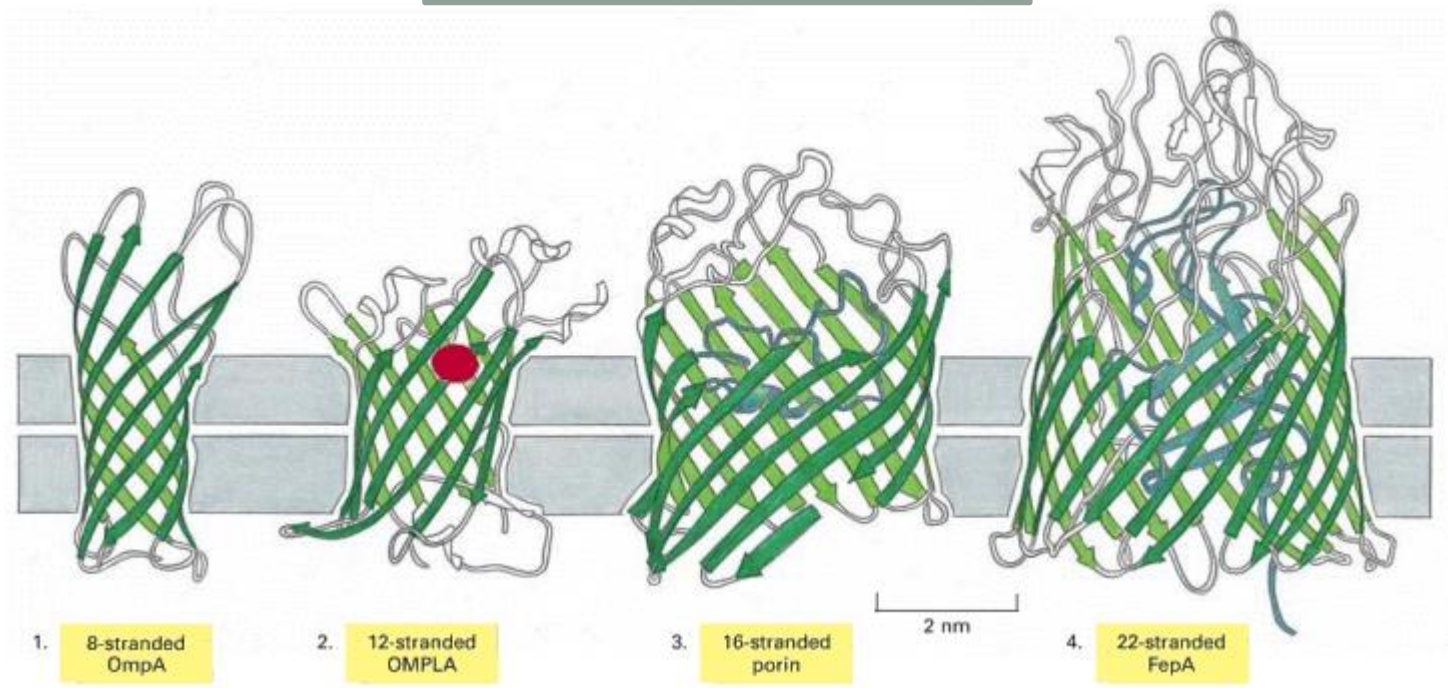
All-β membrane proteins

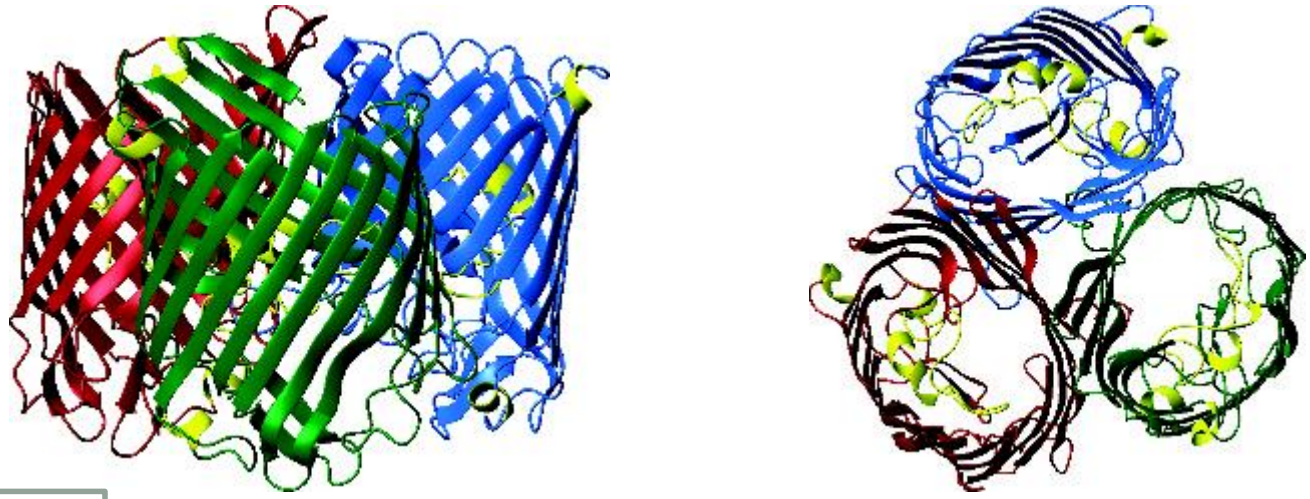
- Tilted strands
  - Longer than ~8-9 residues for each β-strand
- Antiparallel sheets
- Closed β-barrel
  - Edge strands in open sheets cannot be satisfied in membrane
- Hydrophobic sidechains covering exterior surface while polar/charged sidechains facing interior
  - Harder to predict transmembrane strands based on the sequence
- Largely restricted to bacterial, mitochondrial, and chloroplast outer membranes



The transport protein FhuA (PDB 1BY3)

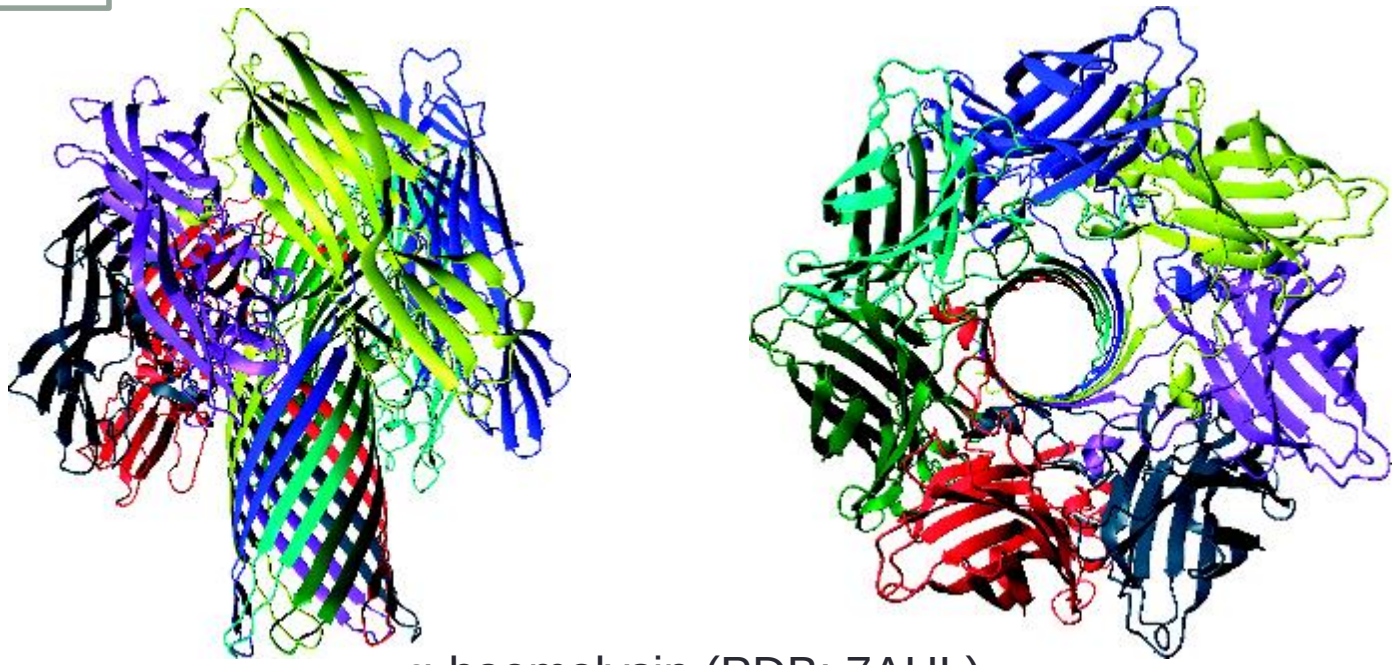
Different sizes of β-barrels





Oligomerization of β-barrels

OmpF (porins) is a trimer of barrels



α-haemolysin (PDB: 7AHL)

Functional roles of transmembrane proteins

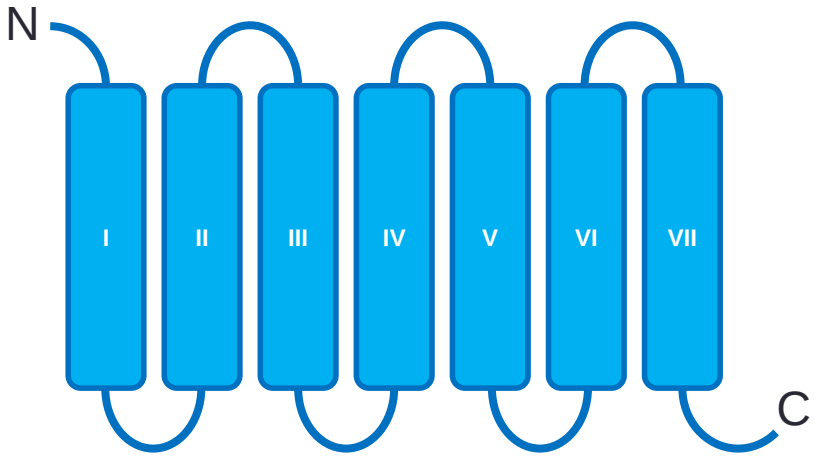
- Receptors
  - GPCR
    - Rhodopsin (http://pdb101.rcsb.org/motm/147)
    - Adrenergic receptor (http://pdb101.rcsb.org/motm/100)
- Channels
  - Potassium channel (http://pdb101.rcsb.org/motm/38)
- Transporters/Pumps
  - ATP synthase (http://pdb101.rcsb.org/motm/72)
- Membrane enzyme
  - Rhomboid protease (http://pdb101.rcsb.org/motm/140)
- Find more in PDB101-”Molecule of the Month”

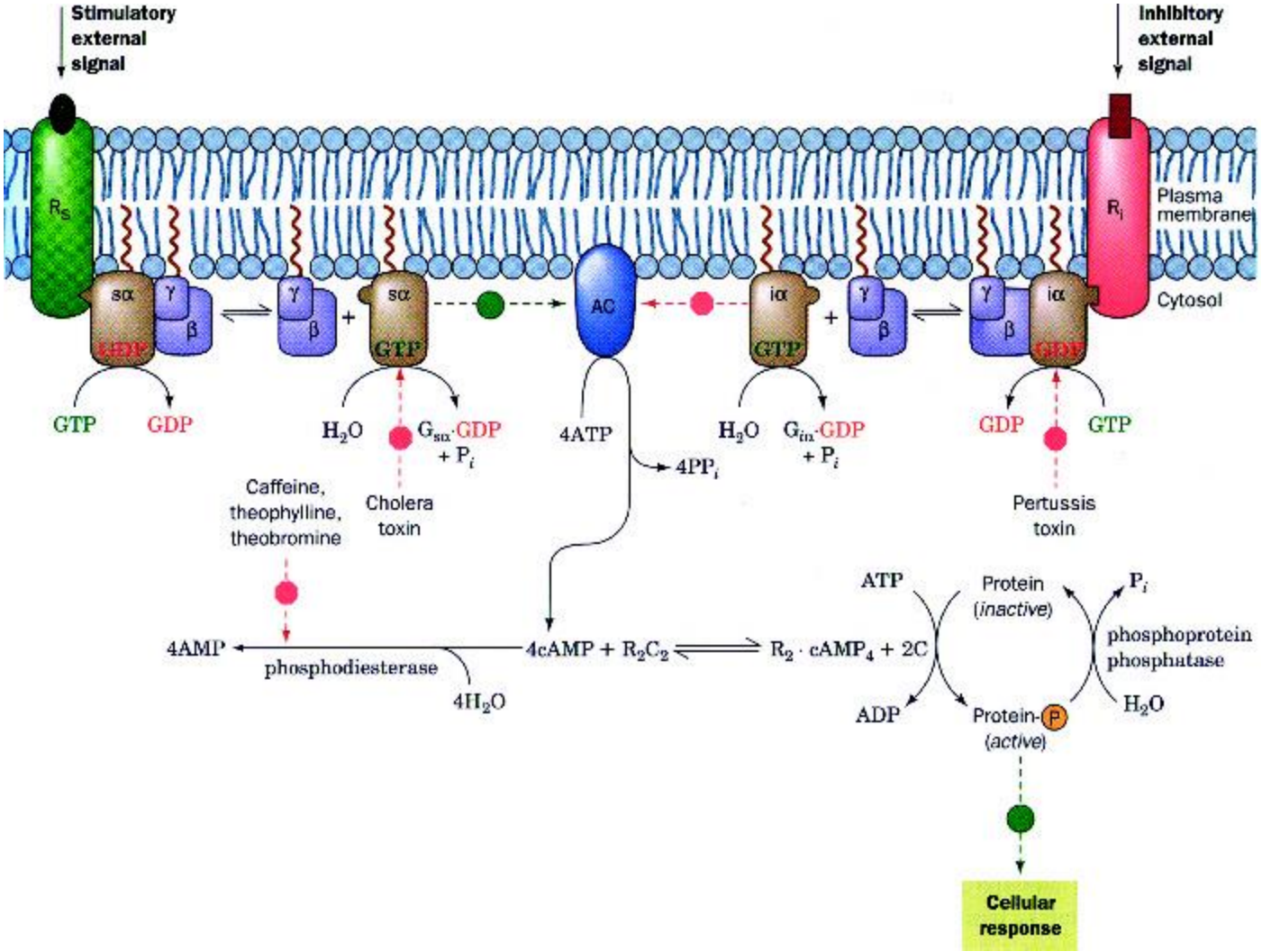
The significance of membrane protein structure

- 1988: Johann Deisenhofer, Robert Huber, and Hartmut Michel (Chemistry) "for the determination of the three-dimensional structure of a photosynthetic reaction centre"
- 1996: Paul D. Boyer, John E. Walker, and Jens C. Skou (Chemistry) "for their elucidation of the enzymatic mechanism underlying the synthesis of adenosine triphosphate (ATP)".
- 2003: Peter Agre and Roderick MacKinnon (Chemistry),
  - MacKinnon "for structural and mechanistic studies of ion channels".
- 2006: Roger Kornberg (Chemistry) "for his studies of the molecular basis of eukaryotic transcription".
- 2009: Venkatraman Ramakrishnan, Thomas A. Steitz, and Ada E. Yonath (Chemistry) "for studies of the structure and function of the ribosome".
- 2012: Robert J. Lefkowitz and Brian K. Kobilka (Chemistry) "for studies of G-protein-coupled receptors".

G-protein coupled receptors (GPCR)

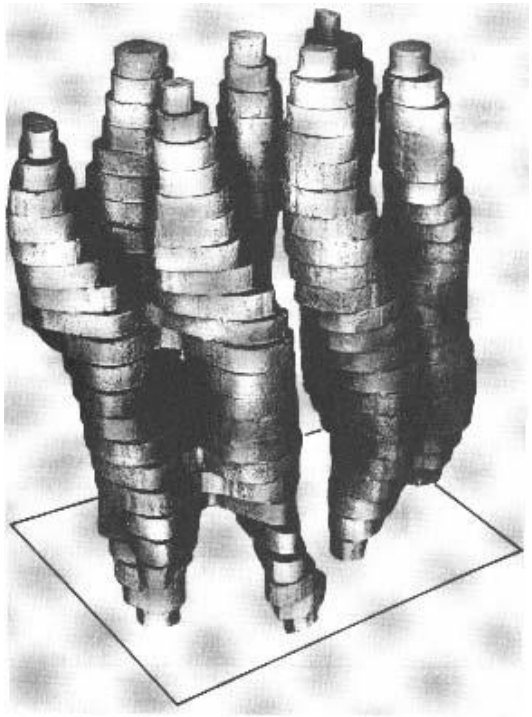
- A large protein family of receptors
  - Sense molecules outside of cell
  - Activate inside signal pathways
- Seven-transmembrane domain receptors
  - Seven transmembrane helices



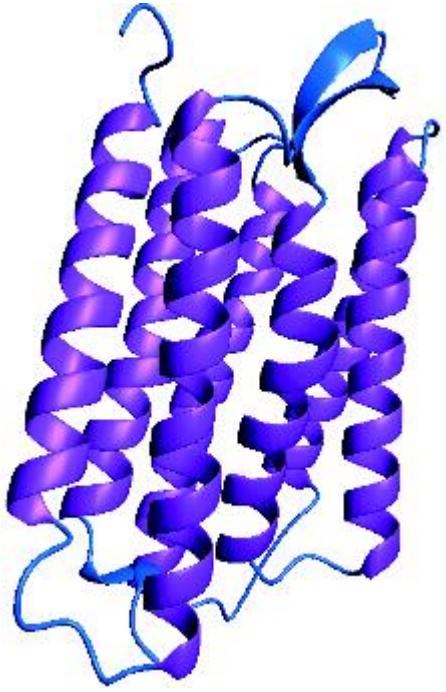

Stimulatory external signal
Inhibitory external signal
R_s
R_i
Plasma membrane
Cytosol
sα
γ
β
GDP
GTP
AC
iα
GTP
GDP
GTP
H_2O
$G_{sα}$·GDP + P_i
4ATP
4PP_i
H_2O
$G_{iα}$·GDP + P_i
GDP
GTP
Caffeine, theophylline, theobromine
Cholera toxin
Pertussis toxin
4AMP
phosphodiesterase
4H_2O
4cAMP + R_2C_2 ⇌ R_2 · $cAMP_4$ + 2C
ATP
Protein (inactive)
P_i
phosphoprotein phosphatase
H_2O
ADP
Protein-P (active)
Cellular response

Rhodopsin

- Rhodopsin is a unique GPCR for photon perception
  - Bacteriorhodopsin (not a real GPCR) and discovery of seven transmembrane helices



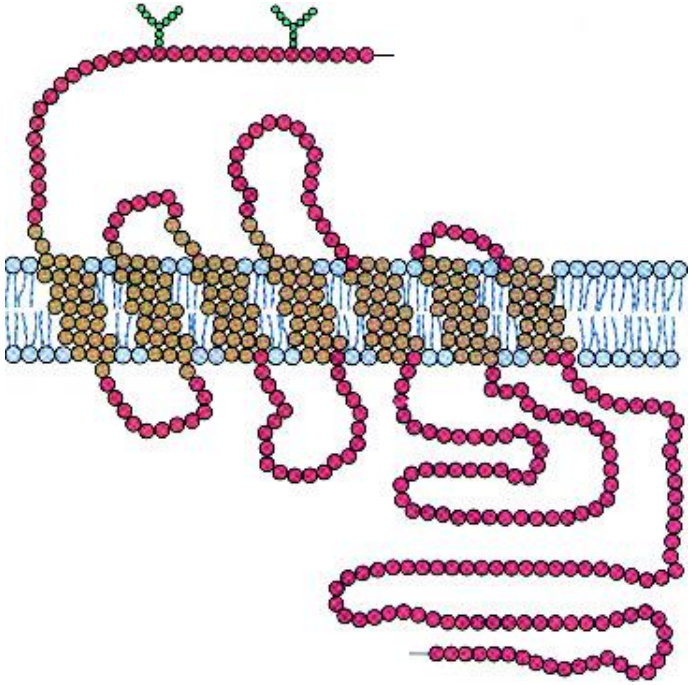
A model proposed for bacteriorhodopsin derived using electron microscopy (*Nature*, 1975)



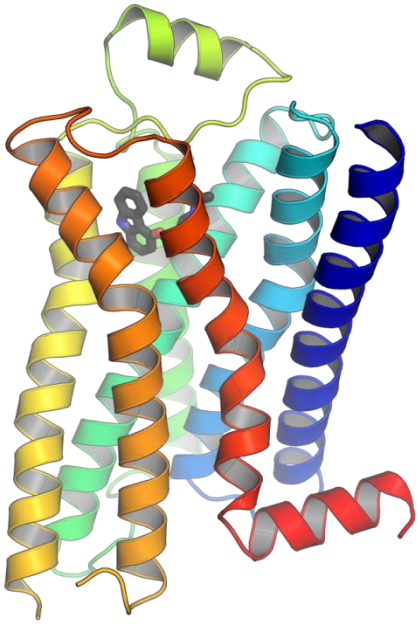
Bacteriorhodopsin (PDB:1C3W)

β_2 adrenergic receptor

- The most studied GPCR, a famous drug target
- Mediating smooth muscle relaxation

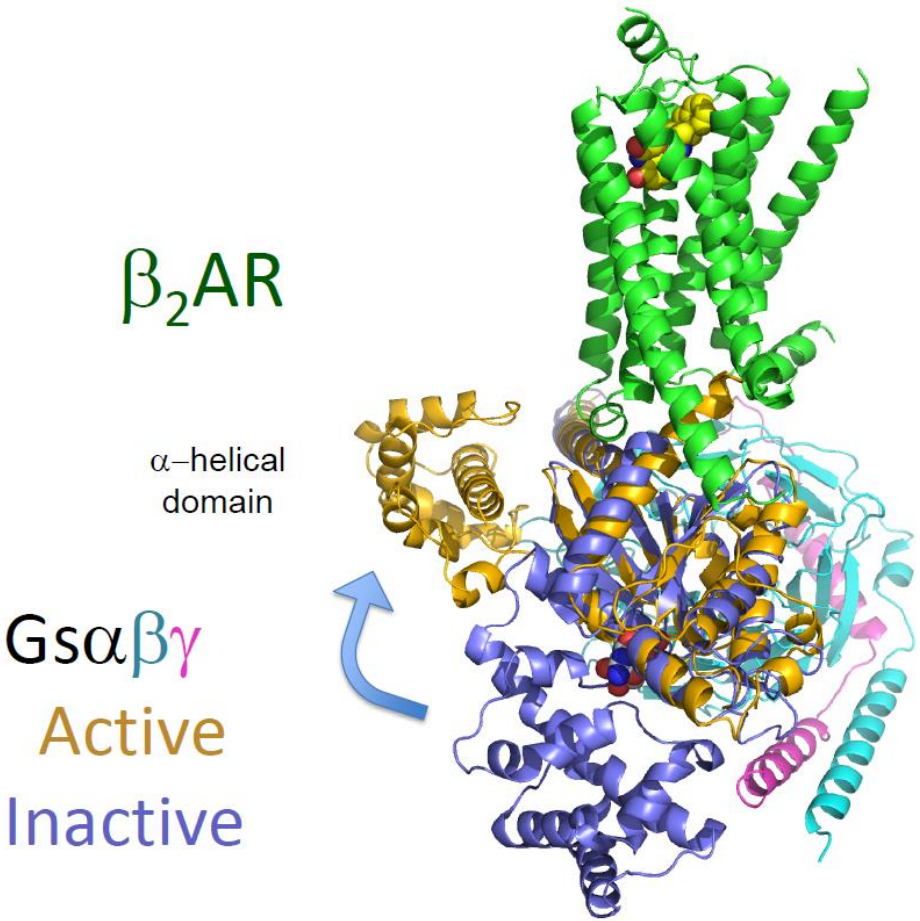


The amino acid sequence of the β_2 adrenergic receptor



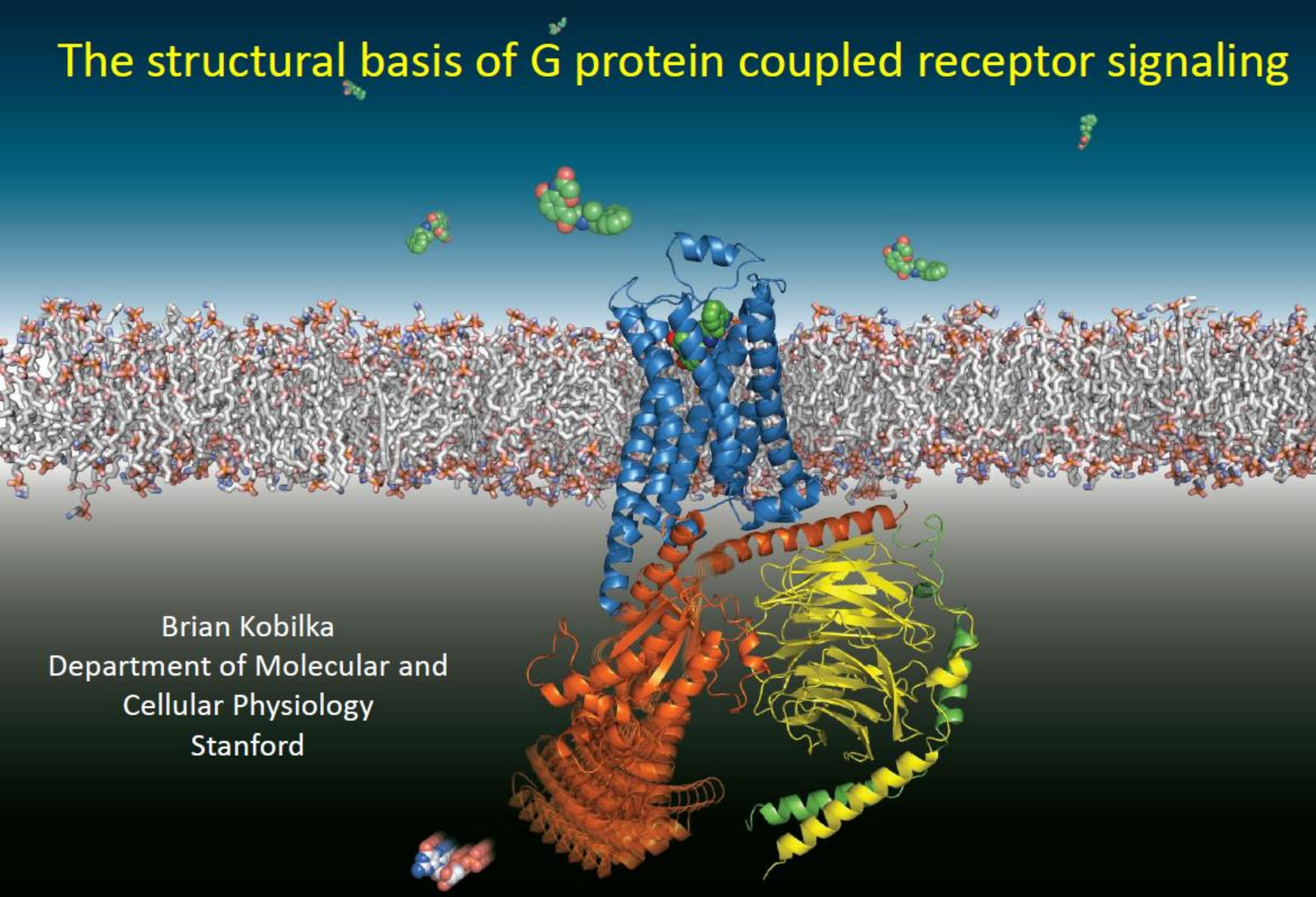
β_2 adrenergic receptor with agonist bound (PDB 2RH1)

β_2 adrenergic receptor in complex with Gs



Kobilka, 2011

The structural basis of G protein coupled receptor signaling

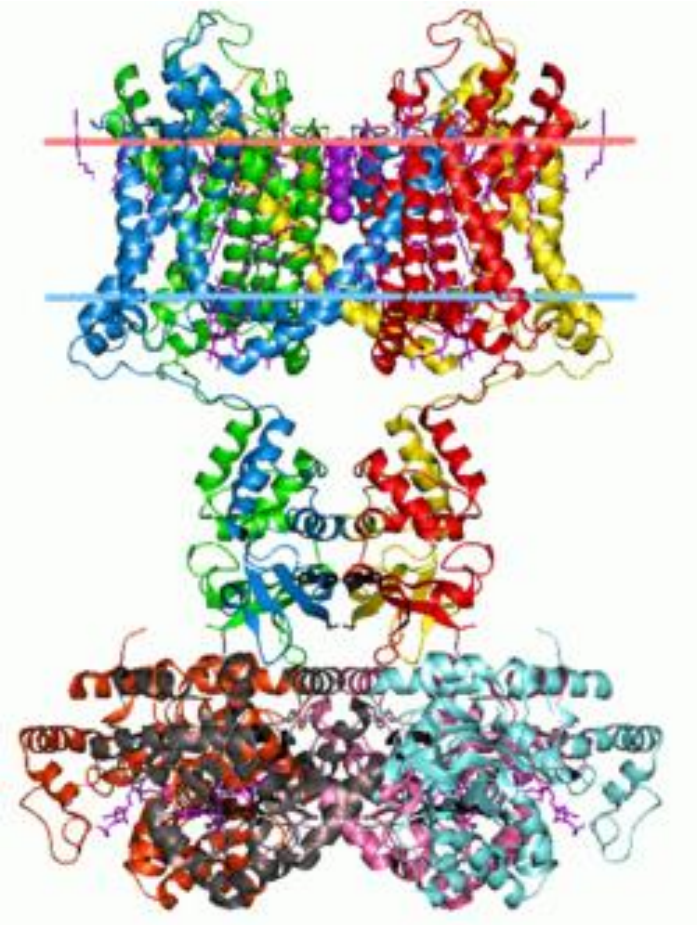


Brian Kobilka
Department of Molecular and
Cellular Physiology
Stanford

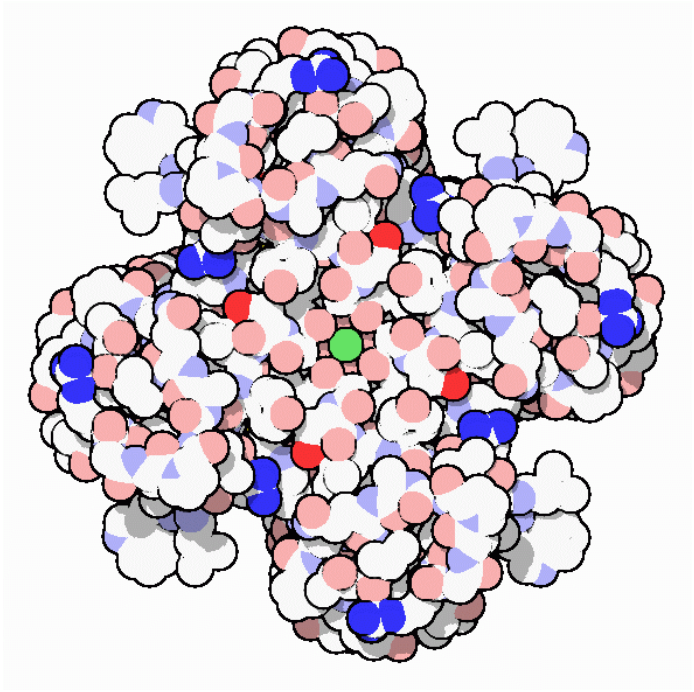
Nobel lecture by Kobilka, 2012

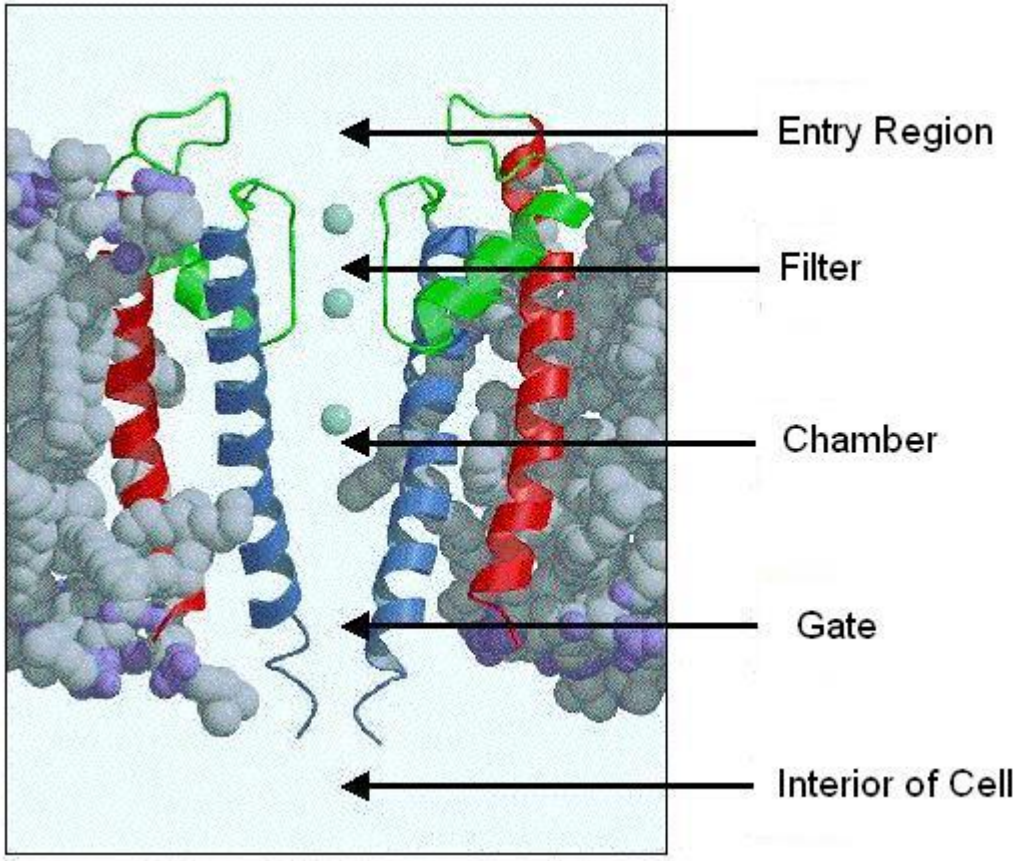
Potassium channel

- Ion channels are the basis for nerve signals propagation
- Potassium channels are designed to allow the flow of potassium ions across the membrane
  - Blocking the flow of other ions, in particular, sodium ions
  - Only one sodium ion to pass for every ten thousand potassium ions



The filter of the channel

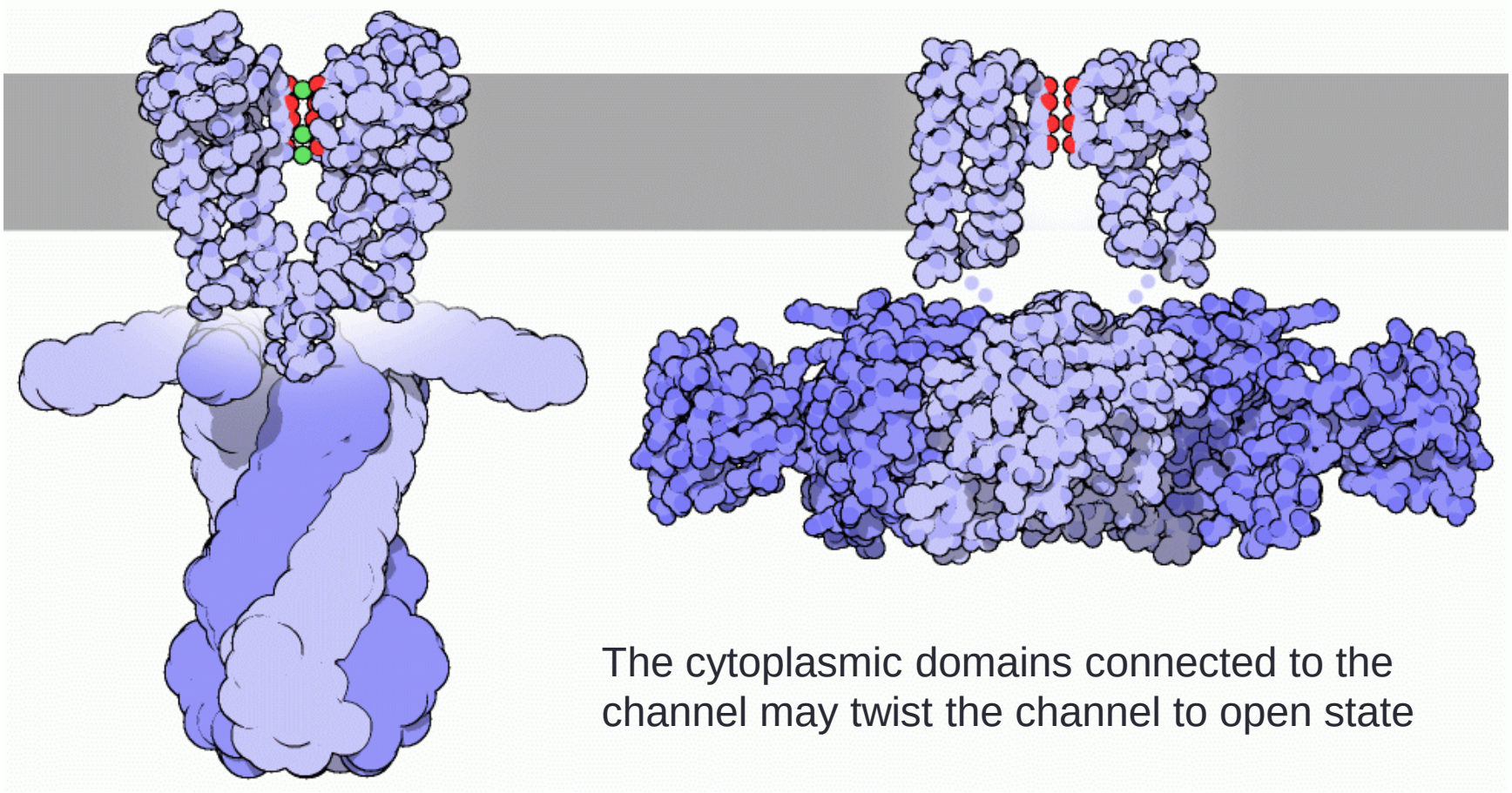




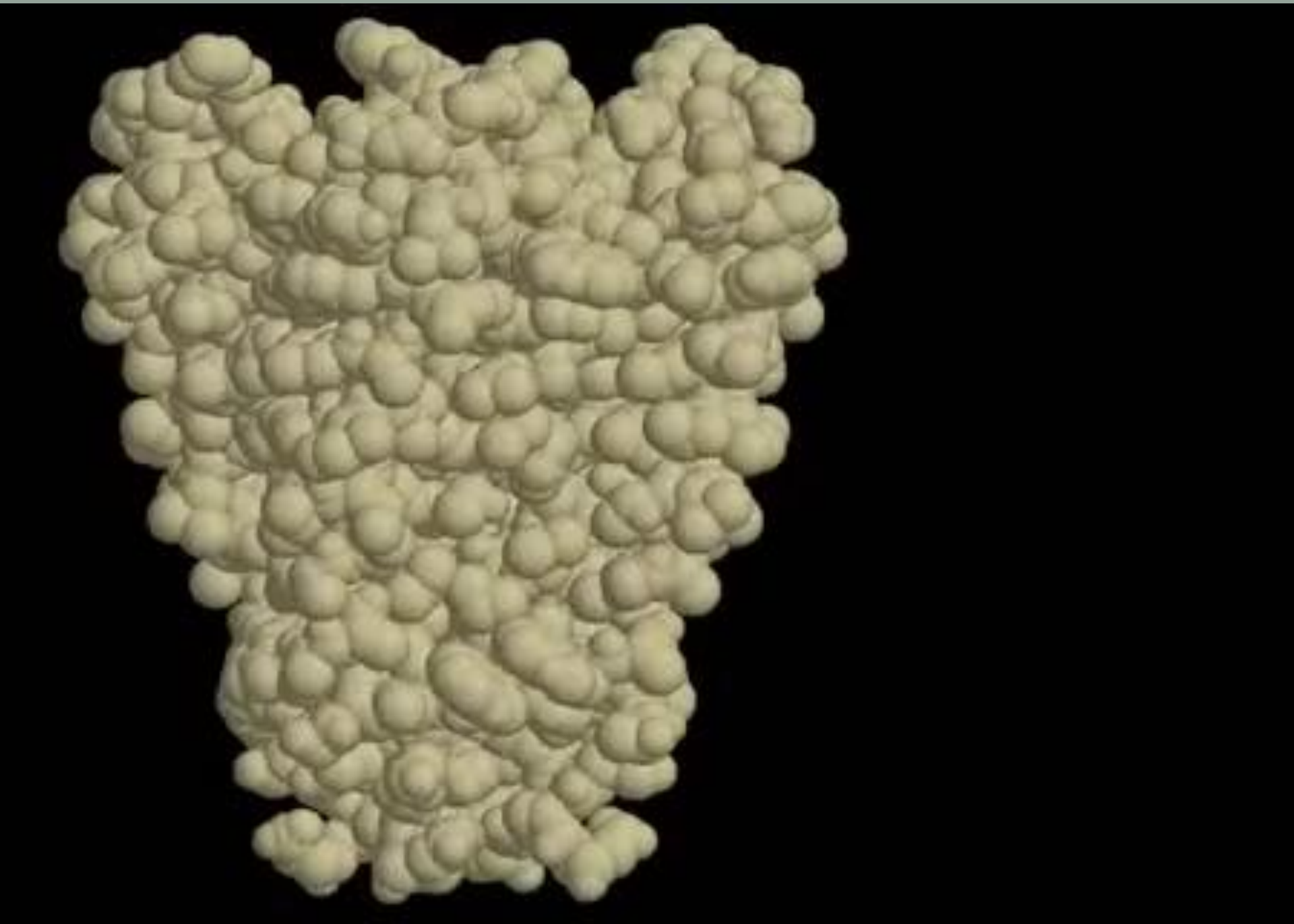
The open of the channel

KcsA in the “close” state

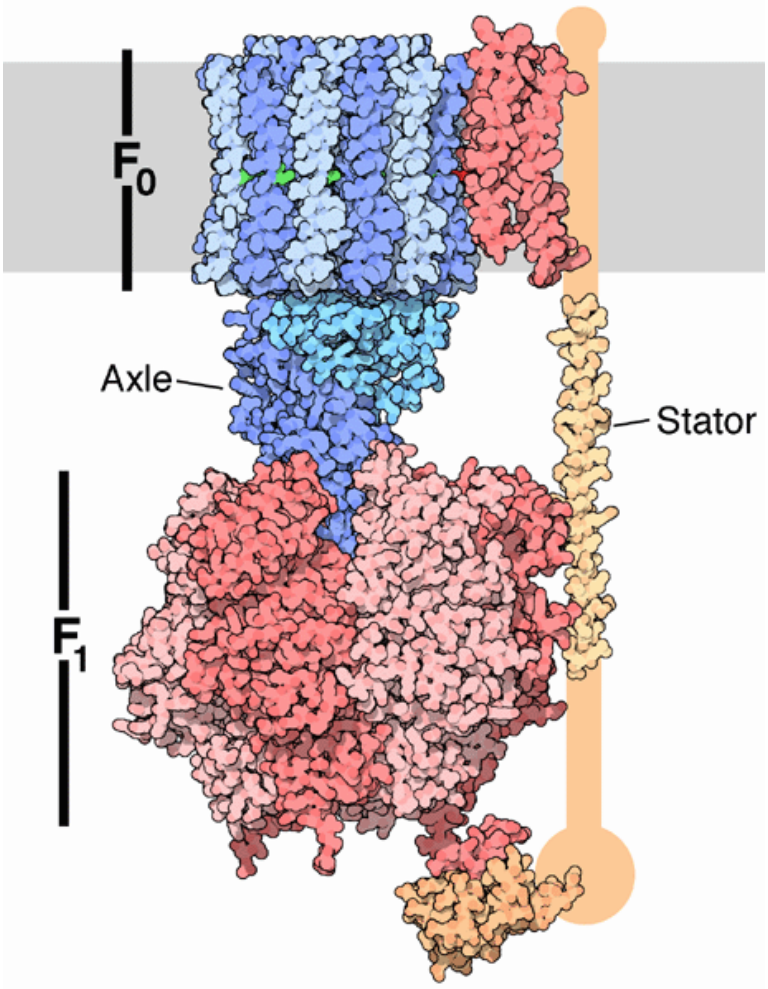
MthK in the “open” state



The cytoplasmic domains connected to the channel may twist the channel to open state



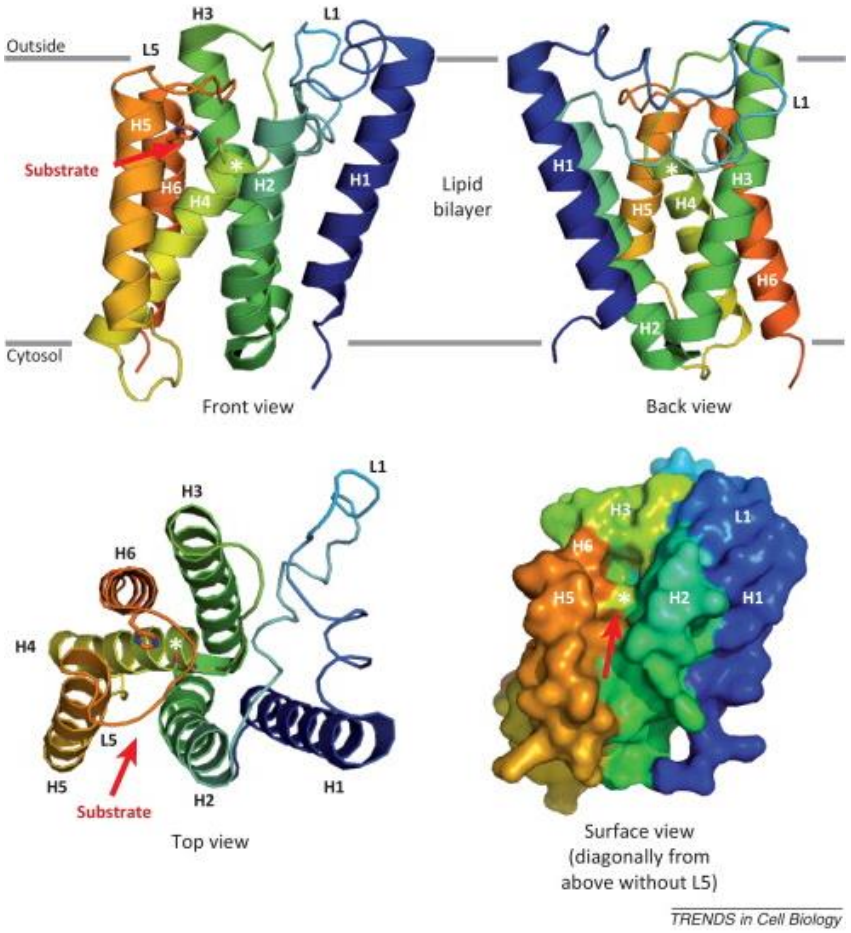
ATP synthase



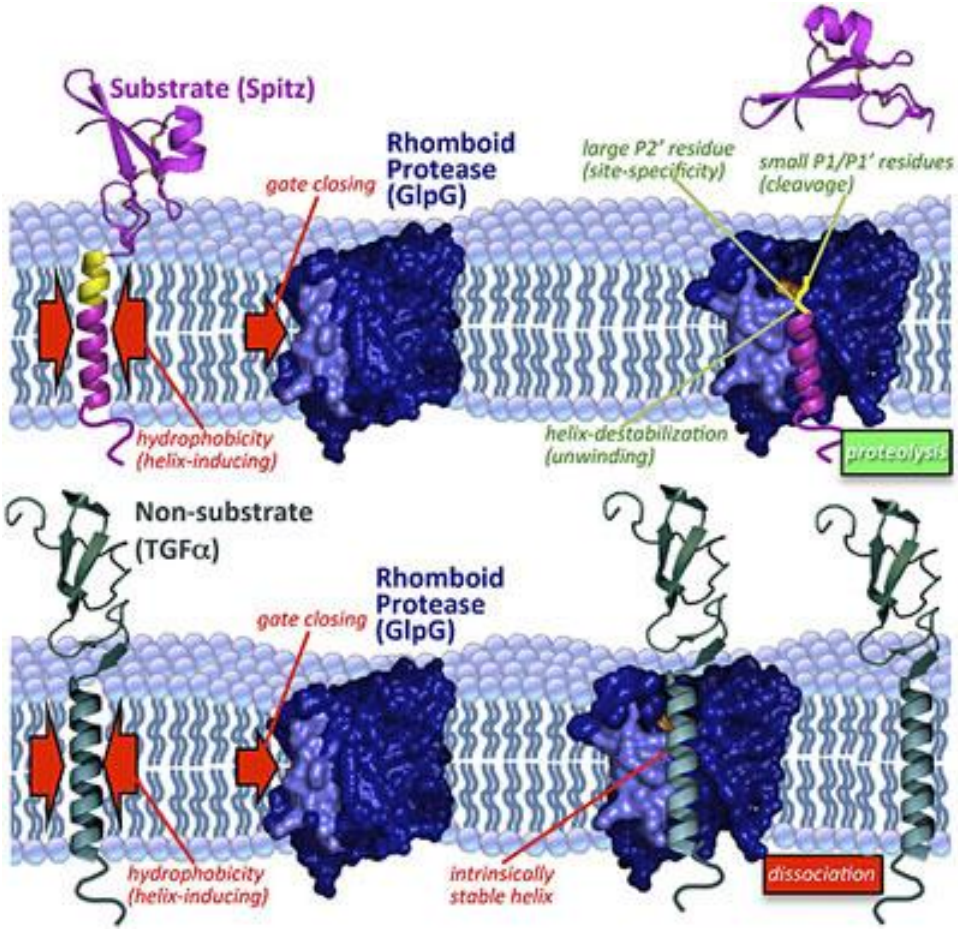
- ATP molecules in cell are generated by ATP synthase
- ATP synthase is an amazing nano-machine
  - enzyme + molecular motor + ion pump
- ATP synthesis is composed of
  - two rotary motors
    - F0, an electric motor
    - F1, a chemical motor
  - a stator

Rhomboid protease

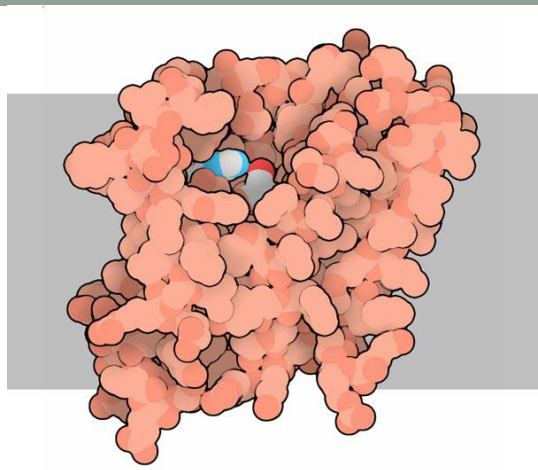
- A serine protease for membrane proteins
- The active site is buried in the membrane
- To release protein domains from membranes by a cut in their membrane anchor

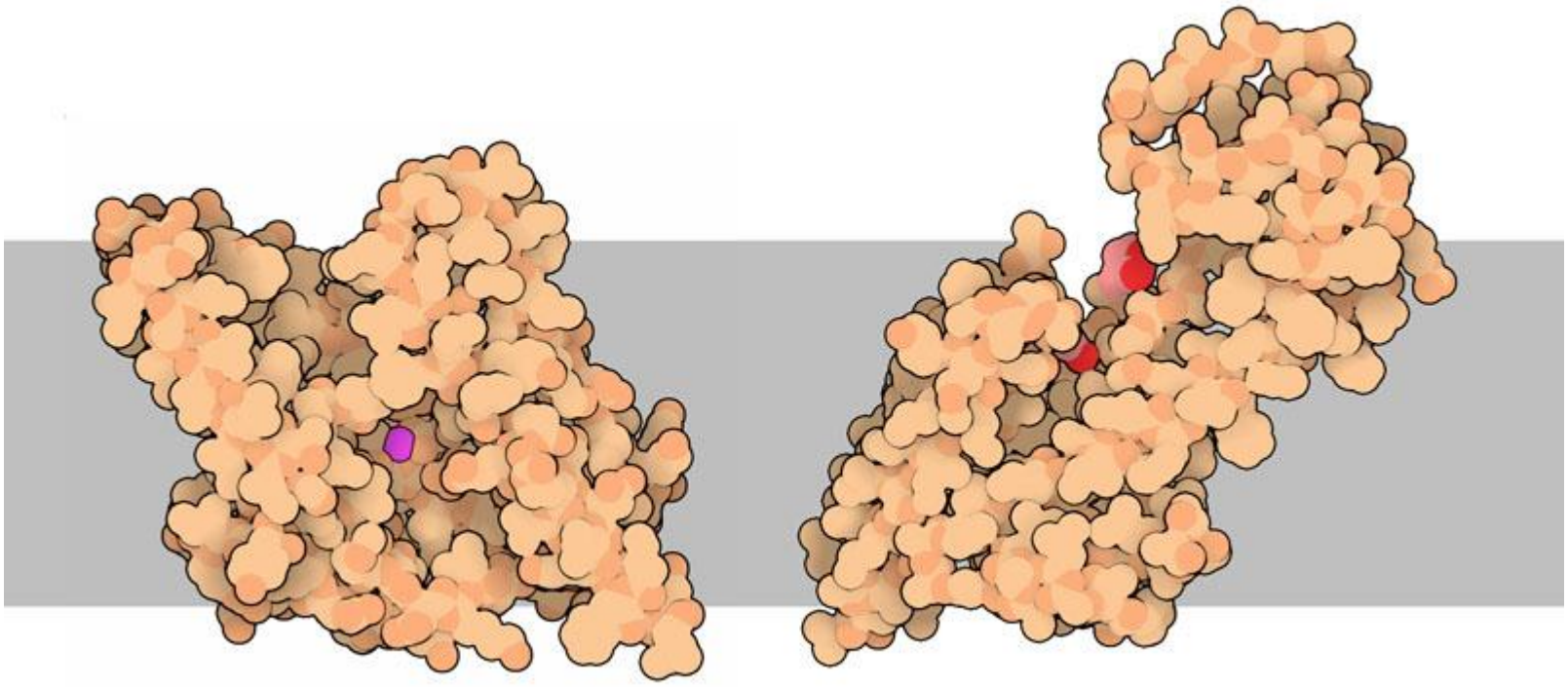


The cleavage mechanism



Intramembrane proteases





Site-2 protease

Preflagellin peptidase FlaK

Generalized membrane proteins