Membrane proteins

- Approximately 30% of proteins in the human genome are predicted to be integral membrane proteins
- Approximately 50% of currently approved drugs target membrane proteins
- Currently ~ 125 unique high-resolution structures of membrane proteins in the PDB

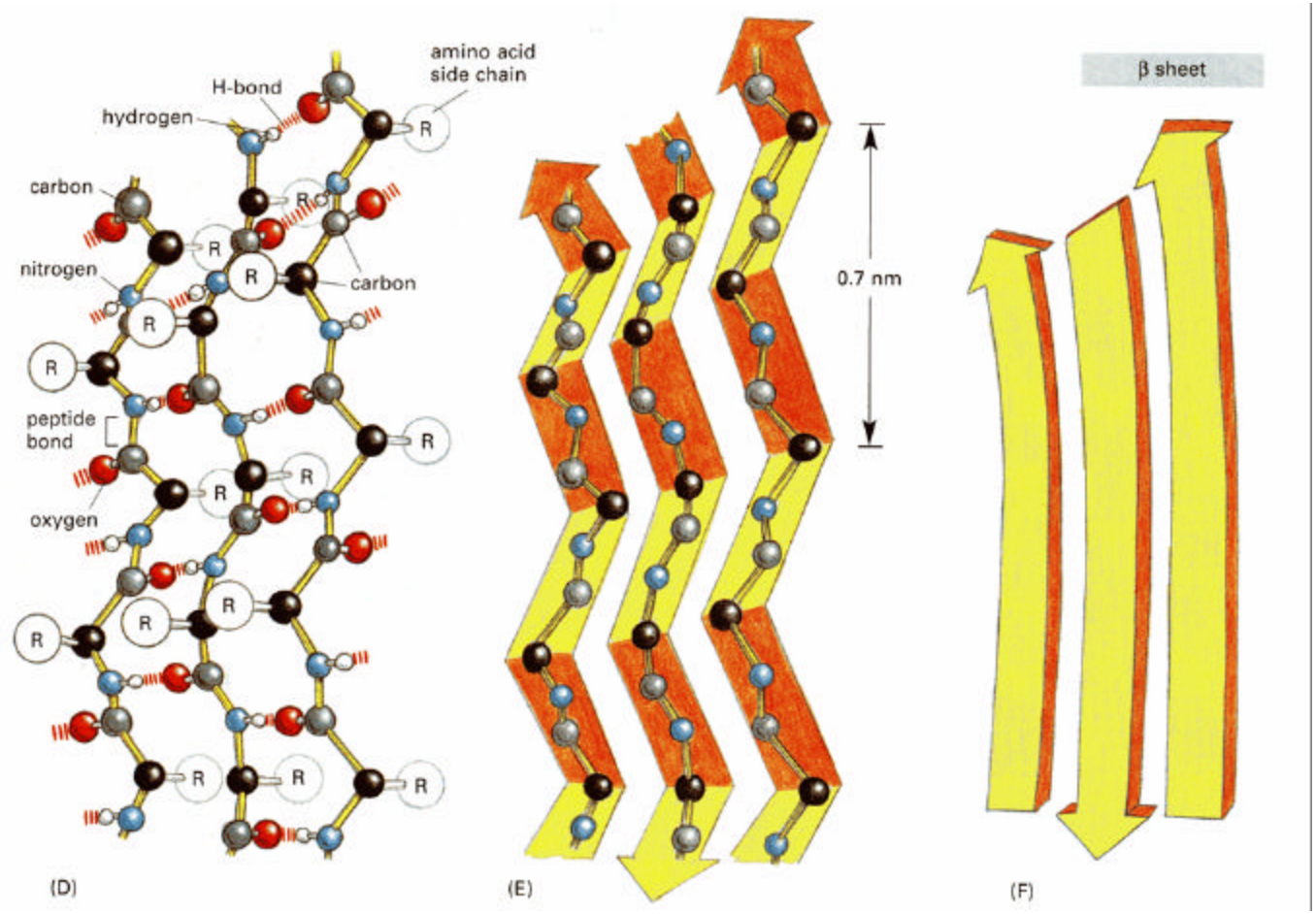
Two structural motifs used to span the membrane:

- Transmembrane a-helix – basic structural unit of eukaryotic membrane proteins and prokaryotic inner membrane proteins. Either single helices or helical bundles.

- Transmembrane ß-strand – found in prokaryotic and mitochondrial membrane proteins. Arranged in a "ß-barrel".

- These structural motifs satisfy the condition of providing H-bonds for all amide and carbonyl groups along the peptide backbone

Transmembrane ß-barrel proteins

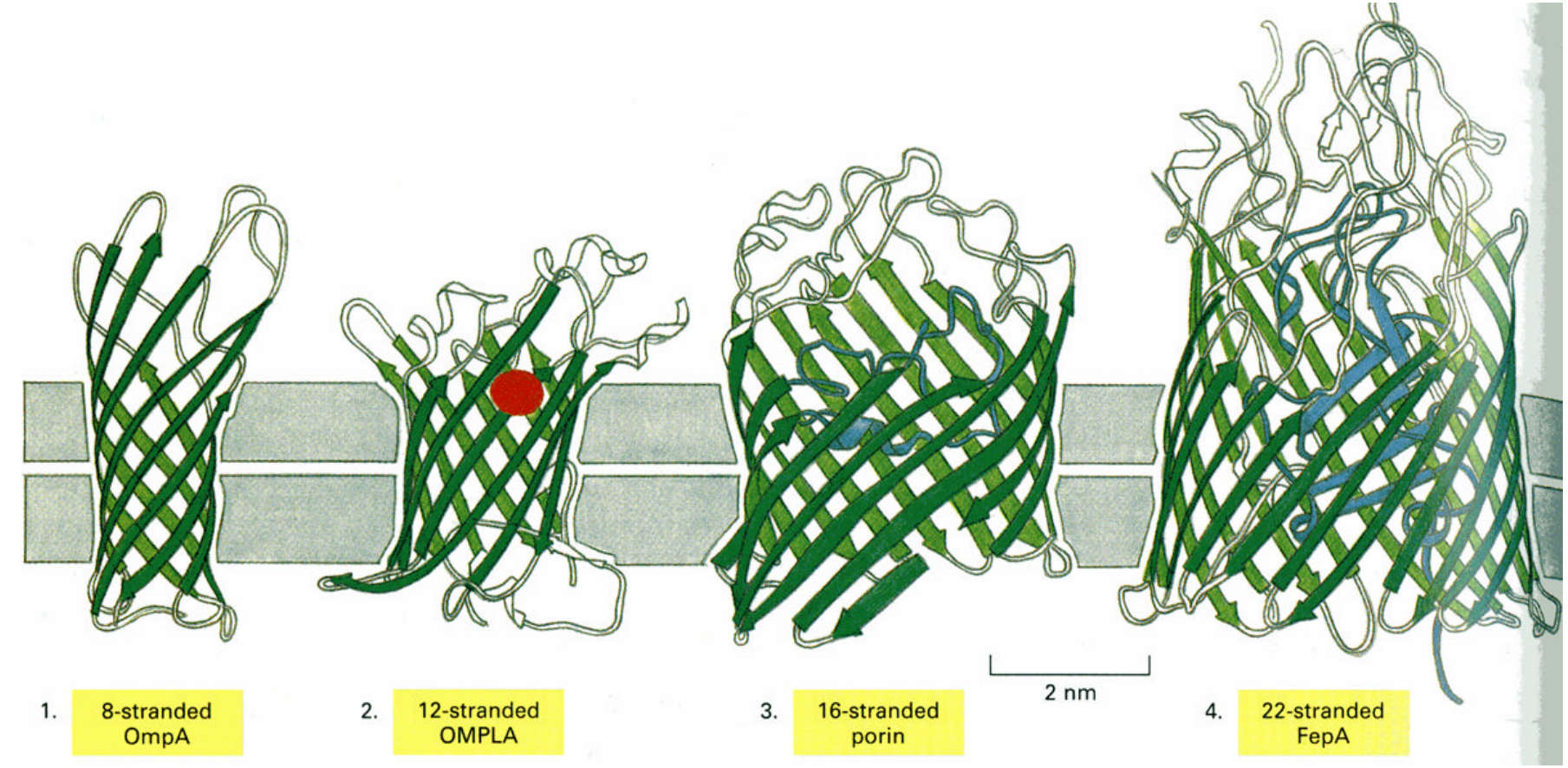


Composed of <u>antiparallel</u> ß-strands

H-bonding between adjacent strands

Hydrophobic side chains face lipid, hydrophilic side chains face interior

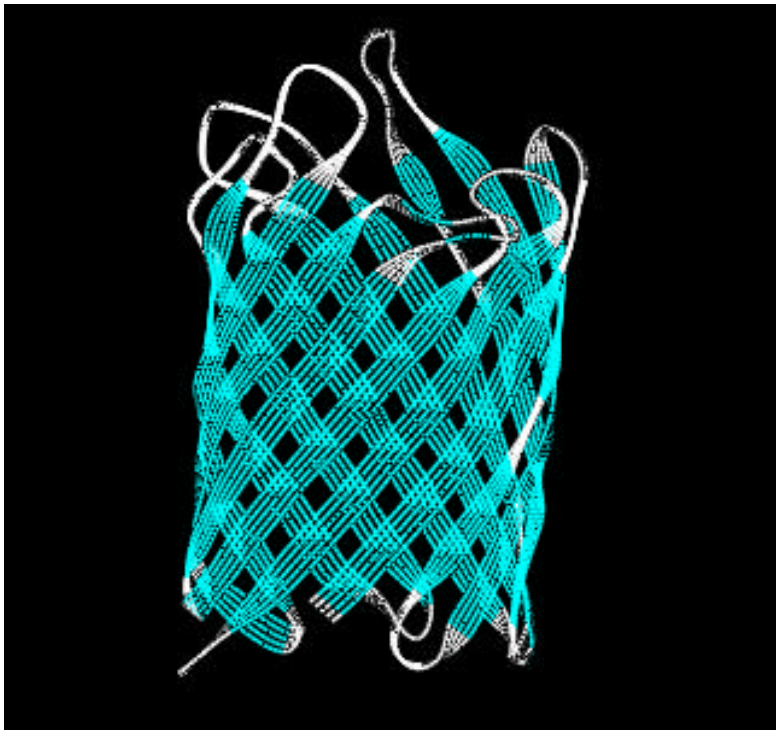
Transmembrane ß-barrel proteins

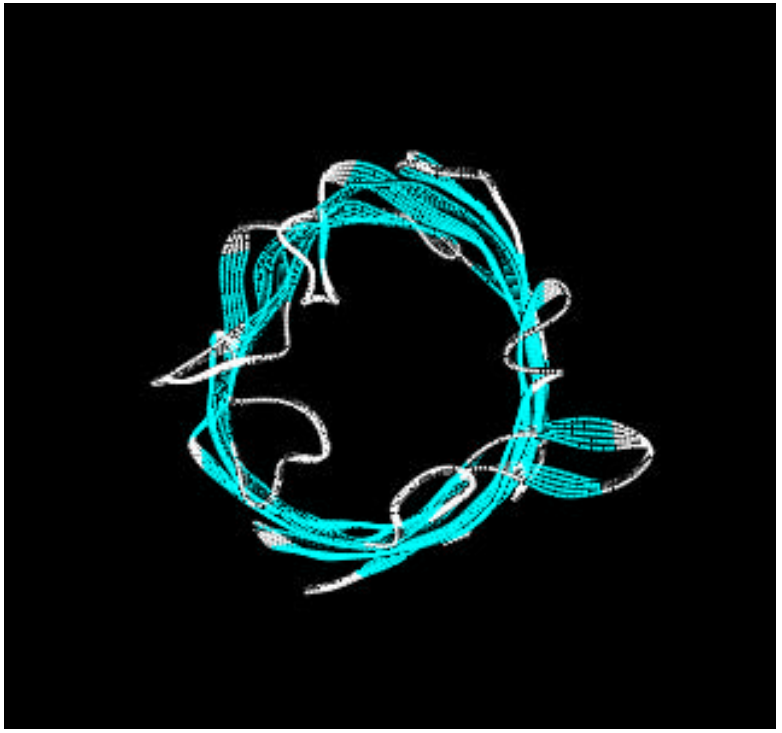


Simple → Complex

Alberts et al., Molecular Biology of the Cell, 4th ed.

Porins – the simplest ß-barrel membrane proteins

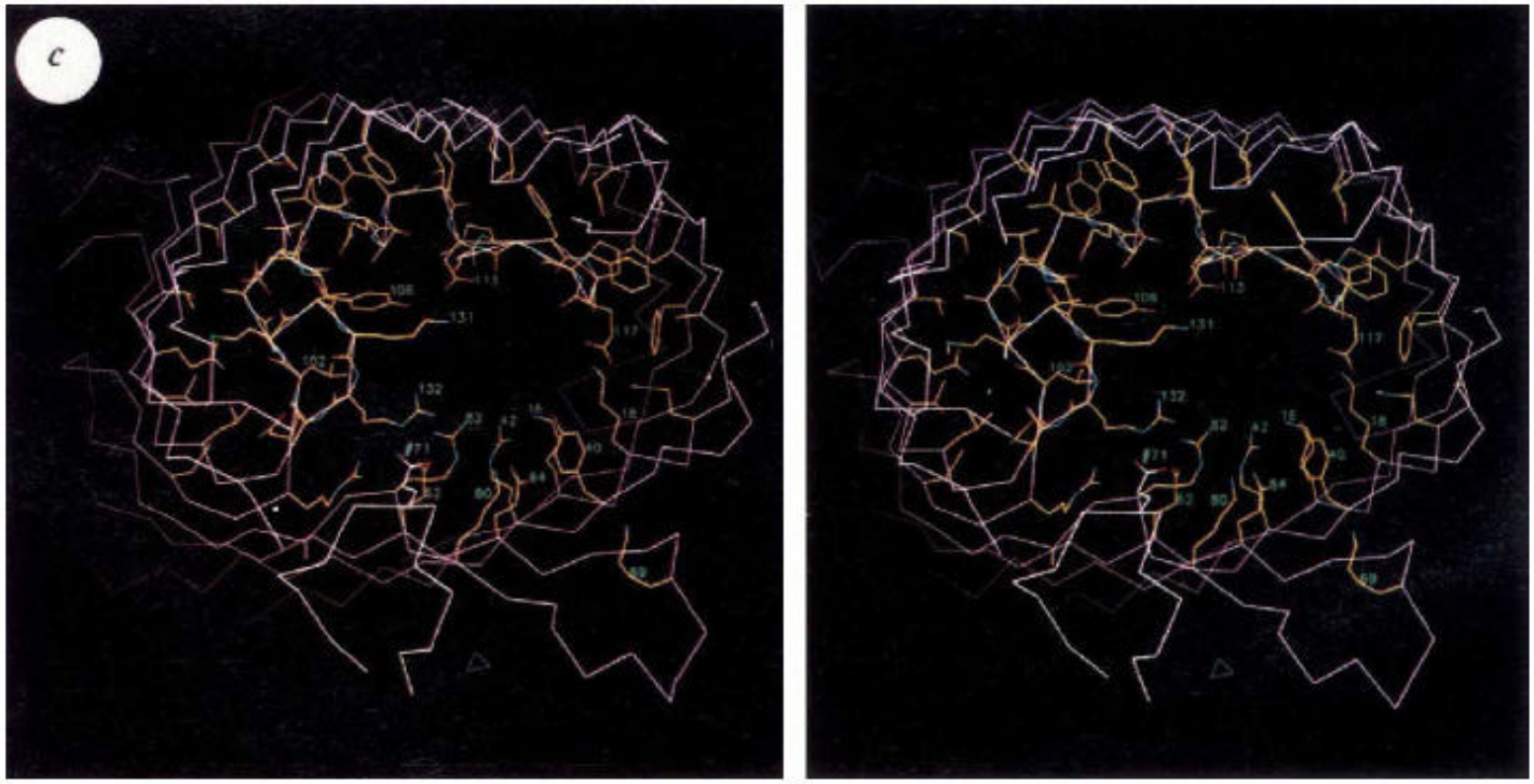




Open, water-filled transmembrane channel. Allow free diffusion of any solute less than ~ 600 Da.

OmpG (2IWV) Yildiz et al., EMBO J. 25(15):3702-13 (2006).
"A monomeric,14-strand ß-barrel from E. coli outer membrane"
crystallized in LDAO, 2.3 Å resolution.

Stereo view of the PhoE channel

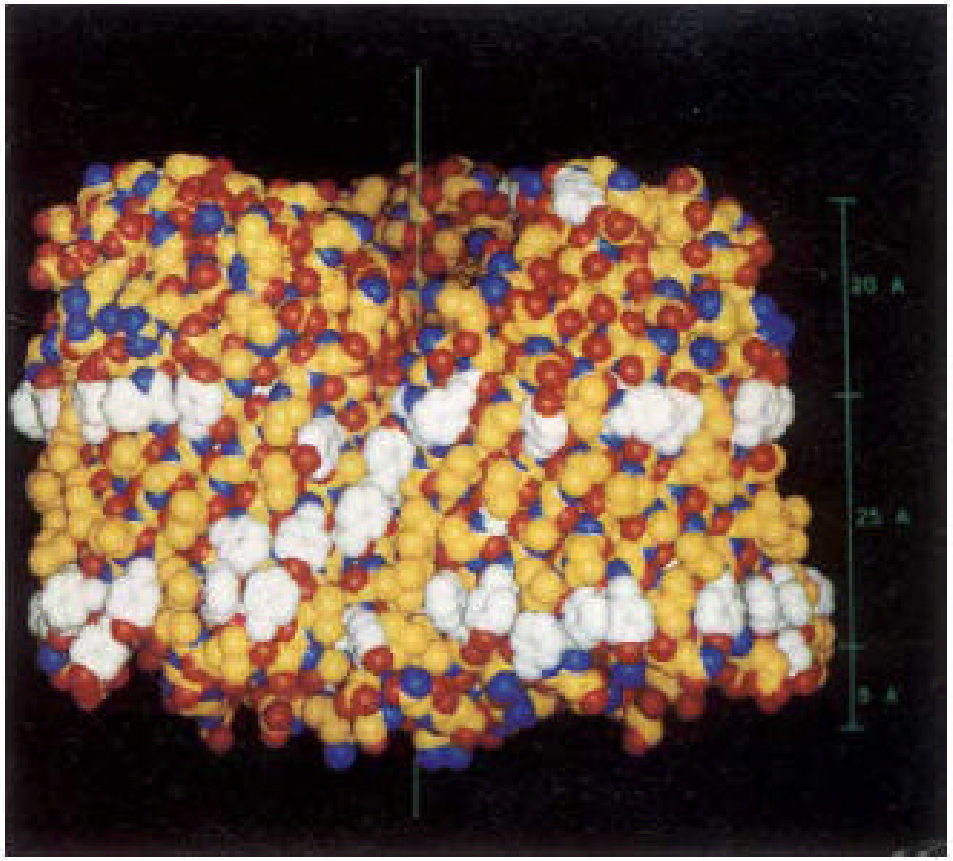


Porin channels are partially blocked by an extracellular loop (usually L3, between 3rd and 4th ß-strands)

In PhoE Lys, Phe residues → anion selectivity (primarily phosphate)

Cowan et al., Nature 358, 727 (1992)

Aromatic residues (Phe, Tyr, Trp) are often found at the membrane interface

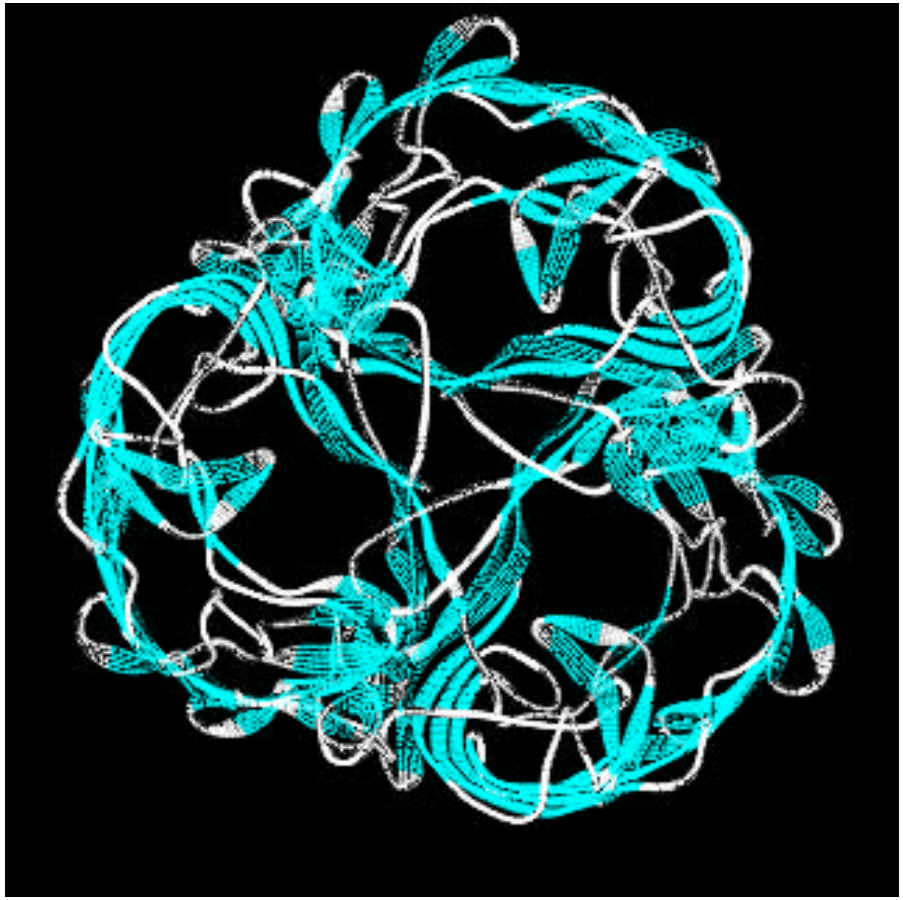


CPK model of the OmpF trimer with aromatic residues in white

Cowan et al., Nature 358, 727 (1992)

Most porins are stable trimers

Maltoporin (LamB) – allows facilitated diffusion of maltoside sugars by providing low-affinity (Kd ~ mM) binding sites along the channel



Meyer et al., J Mol Biol. 266(4):761-75 (1997). PDB 2MPR 2.4 Å.

Facilitated transport through ligand-specific porins

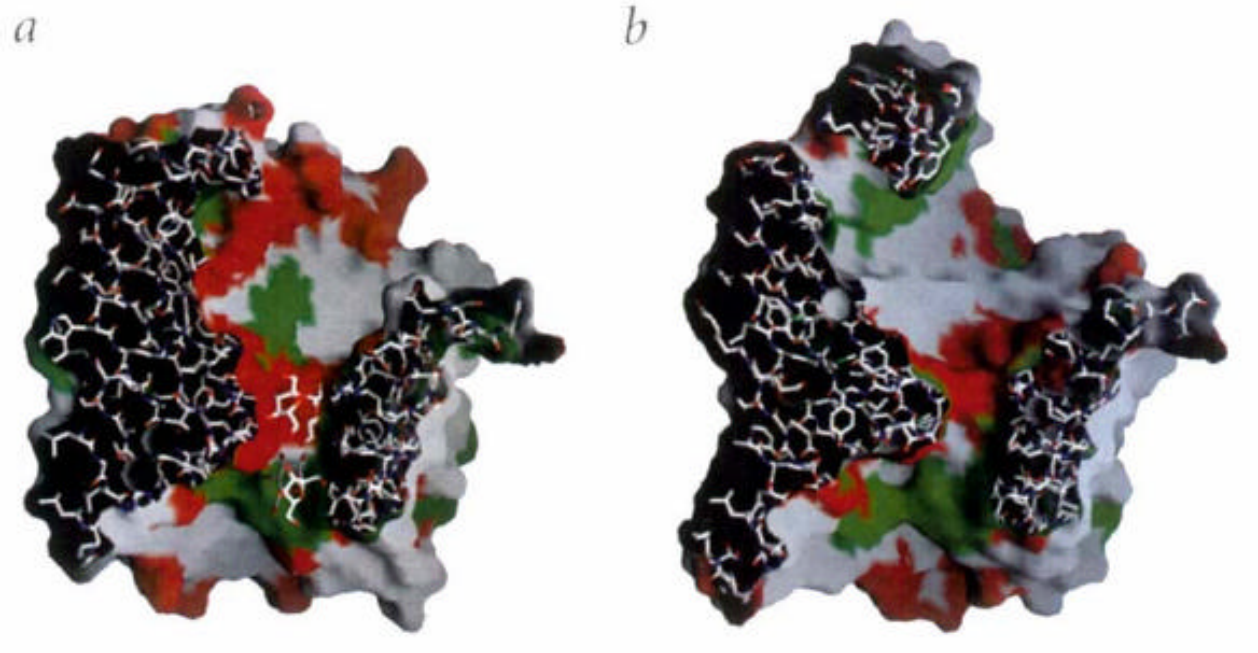


Fig. 4 Images[78] comparing the hourglass-shaped inner channel surfaces of ***a***, ScrY complexed with two sucrose molecules and ***b***, maltoporin. The cutting plane is spanned by the trimer axis and a radial beam connecting the axis and the constriction site center. The molecular surface near Asp, Glu, Arg, Lys is colored red whereas near Phe, Tyr, Trp it is colored green.

Diffusion down a concentration gradient is enhanced by a series of low-affinity binding sites

Forst et al., Nat. Struct. Biol. 5, 37 (1998)

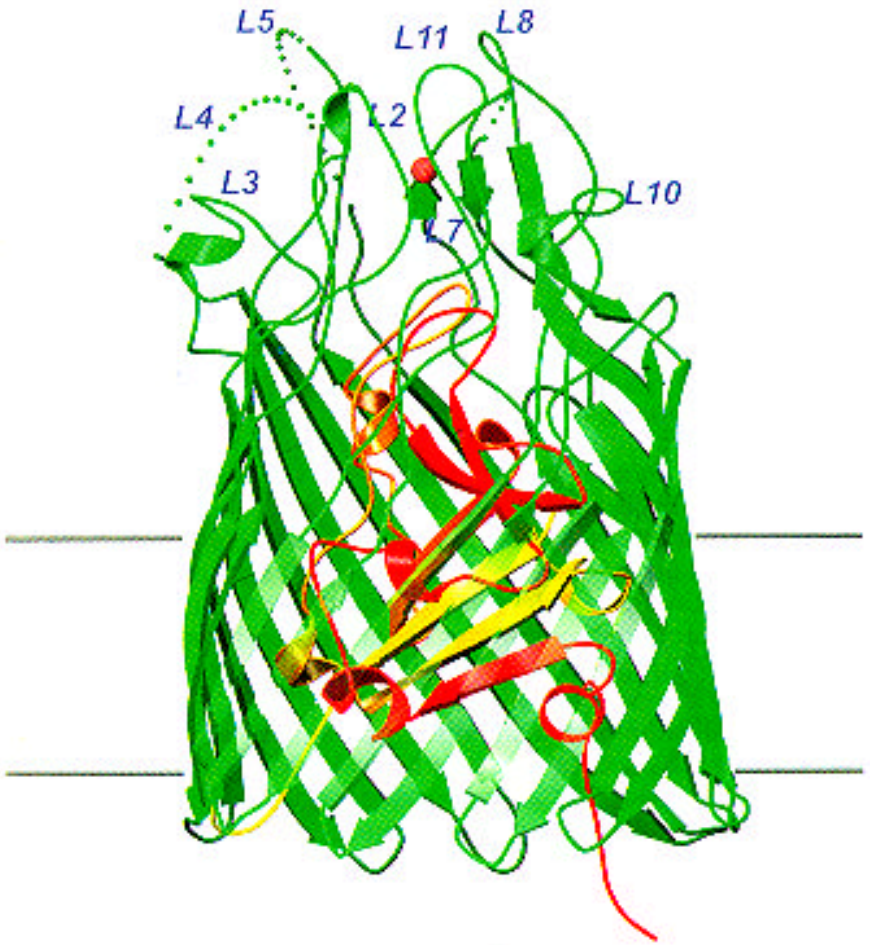
Ligand-specific high affinity transporters

Specific, high affinity
(K_d ~ nM) ligand binding site

Channel completely blocked by a
"core" or "plug" domain

Energy-dependent conformational
change drives ligand transport

Once transported across the OM,
ligand is captured in periplasm
by a specific binding protein
(making transport unidirectional)



Ferric enterobactin receptor, FepA

S.K. Buchanan et al., Nat. Struct. Biol. 6, 56, (1999)

Transmembrane ß-barrel proteins

- All known gram-negative outer membrane proteins are ß-barrel proteins
- Composed of antiparallel ß-strands
- Aromatic residues often found at membrane interface
- Can be non-specific diffusion channels, moderately-specific, low-affinity facilitated diffusion channels, or highly-specific, high affinity energy-dependent transporters

Transmembrane a-helical proteins

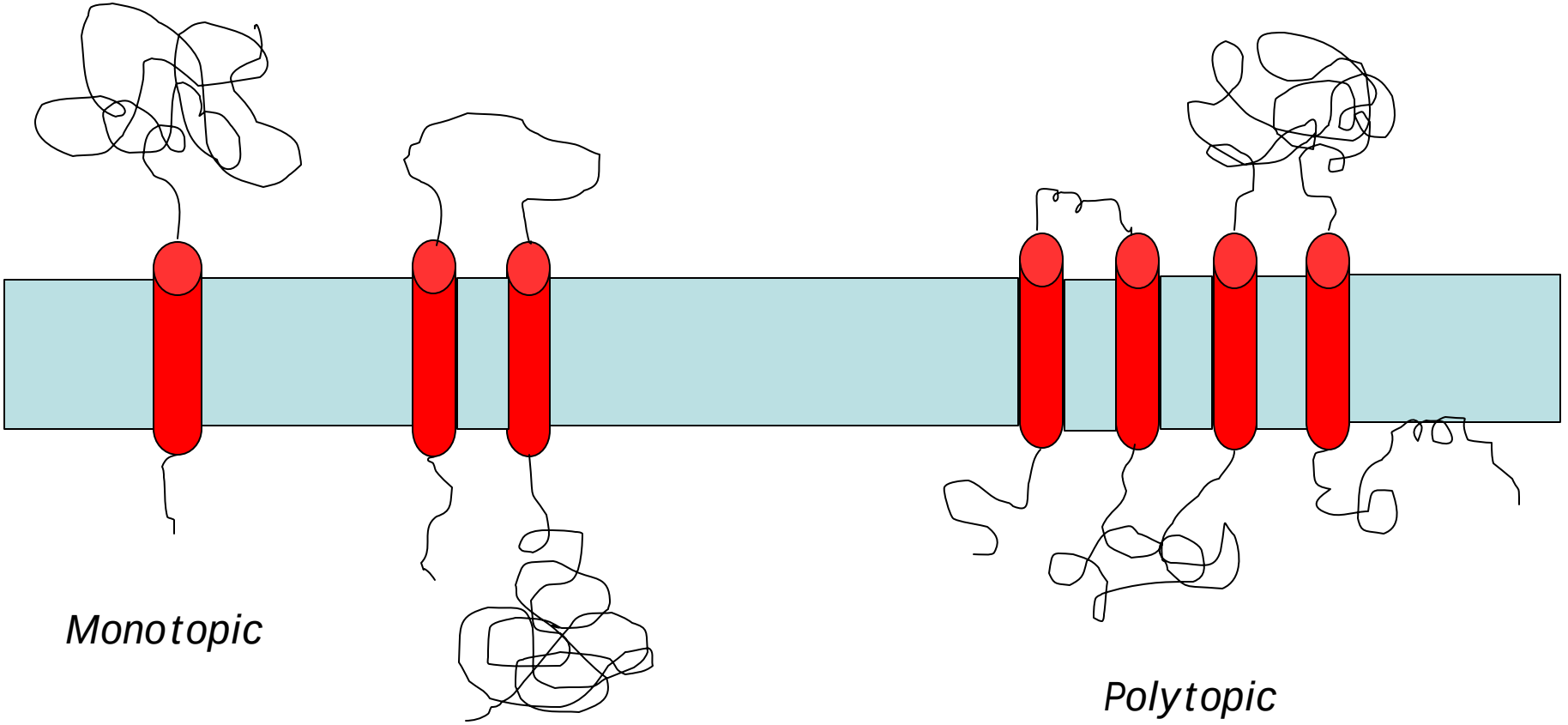
- A minimum of ~ 22 amino acids are required to span the bilayer as an a-helix

  (1.5 Å per residue x 22 = 33 Å, corresponding to the hydrophobic core of the bilayer)

- A majority of the residues will be nonpolar, especially on helical surfaces facing the hydrophobic core of the lipid bilayer

  (hydrophilic residues can be buried inside the helical bundle, sequestered away from the lipid phase)

Helical membrane proteins may contain 1 or many TM helices



Membrane protein structure is driven primarily by the high thermodynamic cost of transferring charged or highly polar residues into the hydrocarbon interior of the bilayer…

1. Most amino acid side chains of the transmembrane segments must be nonpolar (V, L, I, A, M, F), (although hydrophilic residues can be buried inside a helical bundle, sequestered away from the lipid phase)

2. The polar groups of the peptide bond (CO and NH) *must* participate in hydrogen bonds

Mean residue hydrophobicities of buried vs. exposed residues

Transmembrane proteins

	Buried	Exposed
11 RC* helices	0.19	0.48
35 helices**	0.15	0.34

Water-soluble proteins

	Buried	Exposed
37 monomers	0.24	- 0.25
23 oligomers	0.19	- 0.28
7 Hb helices	0.17	- 0.26

* Rhodobacter sphaeroides reaction center

** From sequence analysis of 82 entries including bacteriorhodopsin, GPCRs, sensory transducers, Na and Ca ion channels

Eisenberg hydrophobicity scale (more positive values → more hydrophobic)

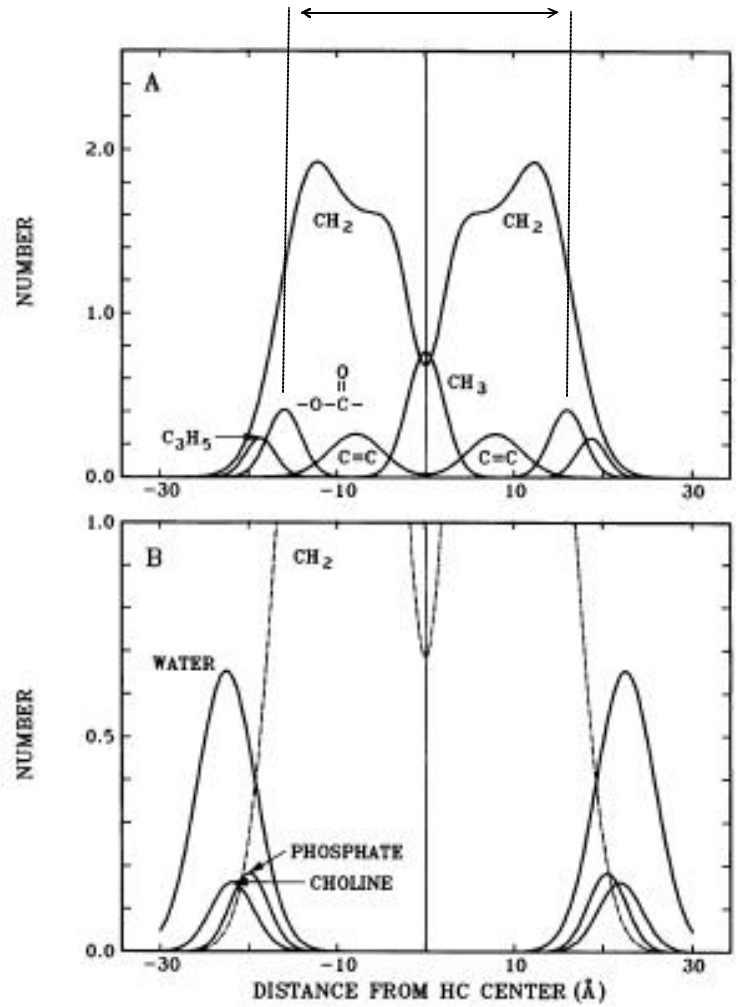
Water-soluble: buried >> exposed Membrane proteins: exposed > buried

Average hydrophobicities of buried residues *are nearly identical* for water-soluble and membrane proteins

Rees et al., Science 245, 510 (1989)

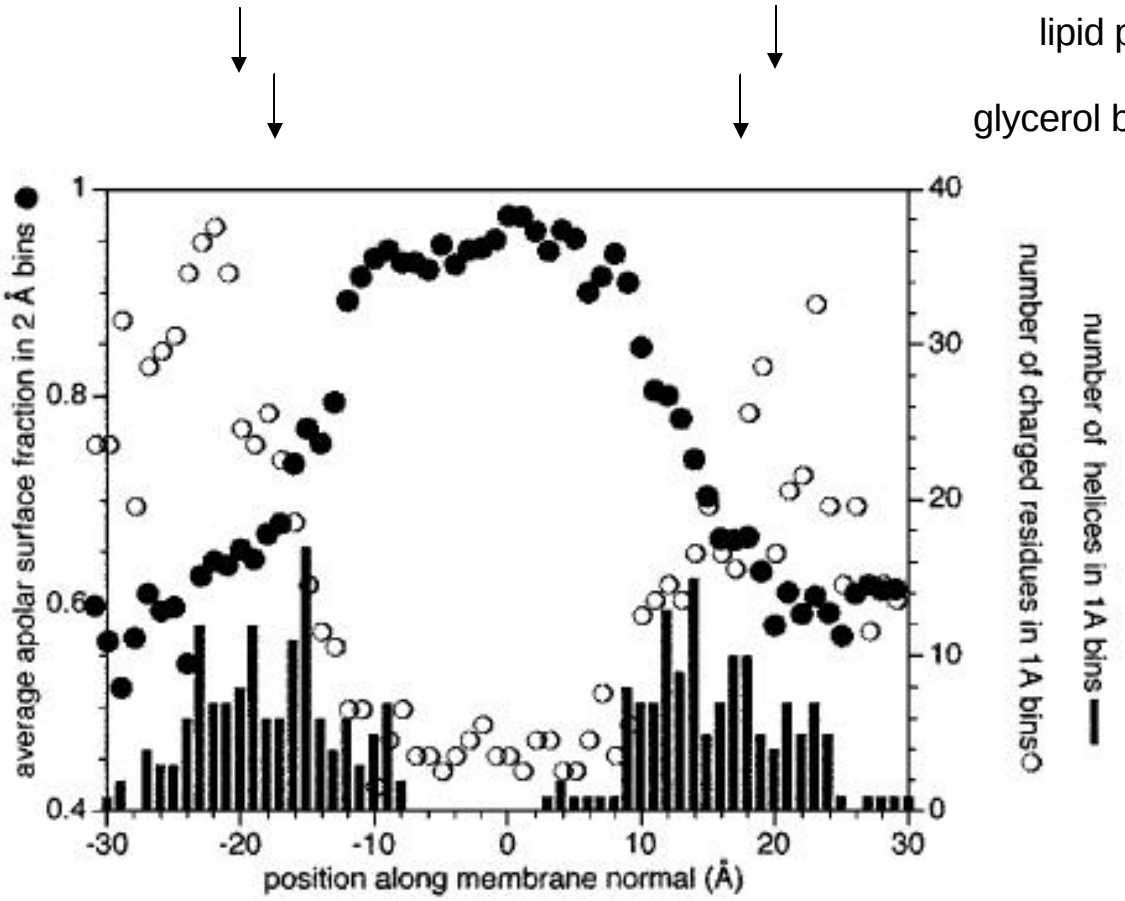
Structure of di (18:1) PC (DOPC)

hydrophobic core
~ 32 – 36 Å



M. C. Wiener and S. H. White, Biophys. J. 61, 434 (1992) “Structure of a fluid dioleoylphosphatidylcholine bilayer determined by joint refinement of x-ray and neutron diffraction data”.

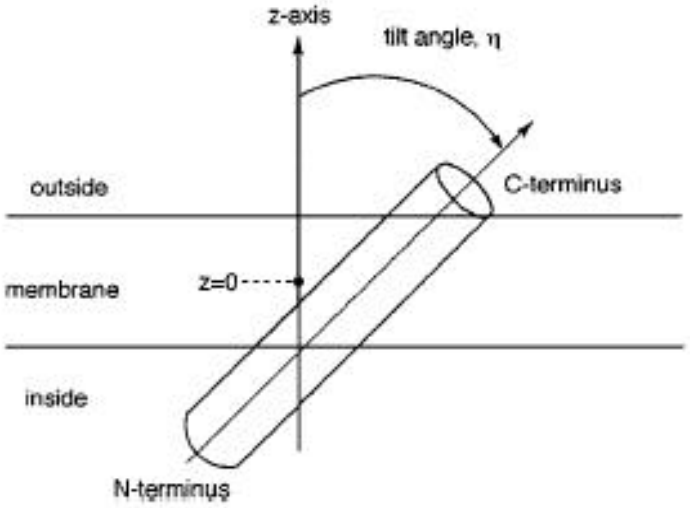
*Alignment of TM helices with lipid bilayer **

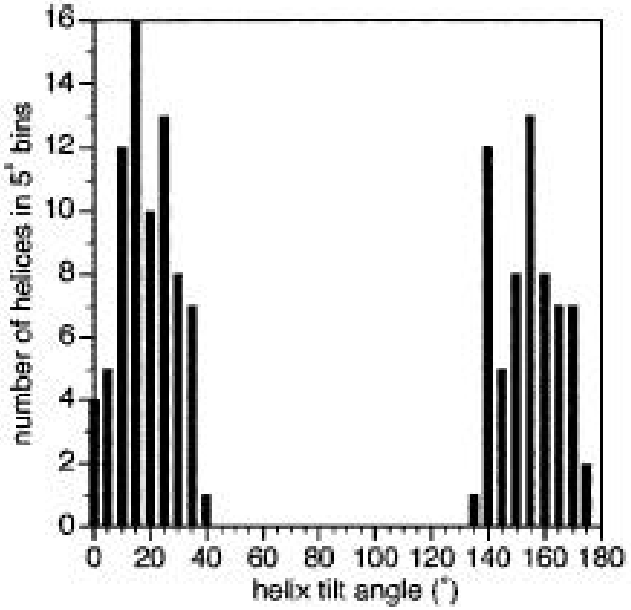


* Based on statistical analysis of 139 TM helices

Spencer, R. H., and D. C. Rees Ann. Rev. Biophys. Biomol. Struct. 31, 207 (2002)

Orientation of TM helices





- Preferred tilt angle of ~ 20°/160° to membrane normal
- Range 0 – 40° (140 – 180°)

Prediction of transmembrane helices from amino acid sequence

- Each amino acid is assigned a numerical value of hydrophobicity based on a given scale (e.g., Kyte and Doolittle, Eisenberg, Wimley and White)

- A moving average is calculated for a given window, (typically ~ 19 amino acids). Peaks indicate likely TM segments

Hydrophobicity scales

Residue	Symbol	CCS	Kyte-Doolittle	Eisenberg
		Hi	**Hi**	**Hi**
Ile	I	**8.7**	**4.5**	**0.73**
Leu	L	9.7	3.8	0.53
Trp	W	9.7	-0.9	0.37
Phe	F	**10.0**	2.8	0.61
Val	V	4.1	4.2	0.54
Met	M	4.6	1.9	0.26
Tyr	Y	2.5	-1.3	0.02
Ala	A	-1.1	1.8	0.25
Pro	P	-0.2	-1.6	-0.07
Thr	T	-3.8	-0.7	-0.18
Ser	S	-4.3	-0.8	-0.26
Cys	C	-2.3	2.5	0.04
Gly	G	-2.4	-0.4	0.16
Asn	N	-7.1	-3.5	-0.64
Asp	D	-8.3	-3.5	-0.72
Gln	Q	-6.0	-3.5	-0.69
Glu	E	-8.3	-3.5	-0.62
His	H	-3.8	-3.2	-0.40
Lys	K	-9.9	-3.9	-1.10
Arg	R	**-10**	**-4.5**	**-1.80**

Kyte J., Doolittle R., (1982) “A simple method for displaying the hydropathic character of a protein”. J. Mol. Biol., 157: 105-132.

Eisenberg D., Weiss R.M., Terwilliger C.T., Wilcox W., (1982) “Hydrophobic moments and protein structure”, Faraday Symp. Chem. Soc. 17:109-120.

Tossi, A., Sandri, L, Giangaspero, A. (2002) “New consensus hydrophobicity scale extended to non-proteinogenic amino acids”. In Peptides 2002: Proceedings of the twenty-seventh European peptide symposium. Edizioni Ziino, Napoli, Italy. pp. 416-417

Biology WorkBench 3.2 - GREASE - Microsoft Internet Explorer

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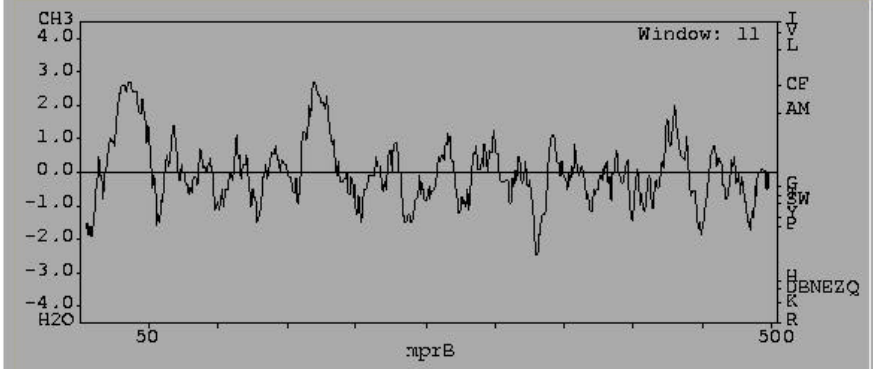
Address http://seqtool.sdsc.edu/CGI/BW.cgi#!

Go

Google Go Bookmarks 6 blocked Check AutoLink AutoFill Send to

Kyte-Doolittle graphical plot

Download a PostScript version of the output



Return Help Report Bugs

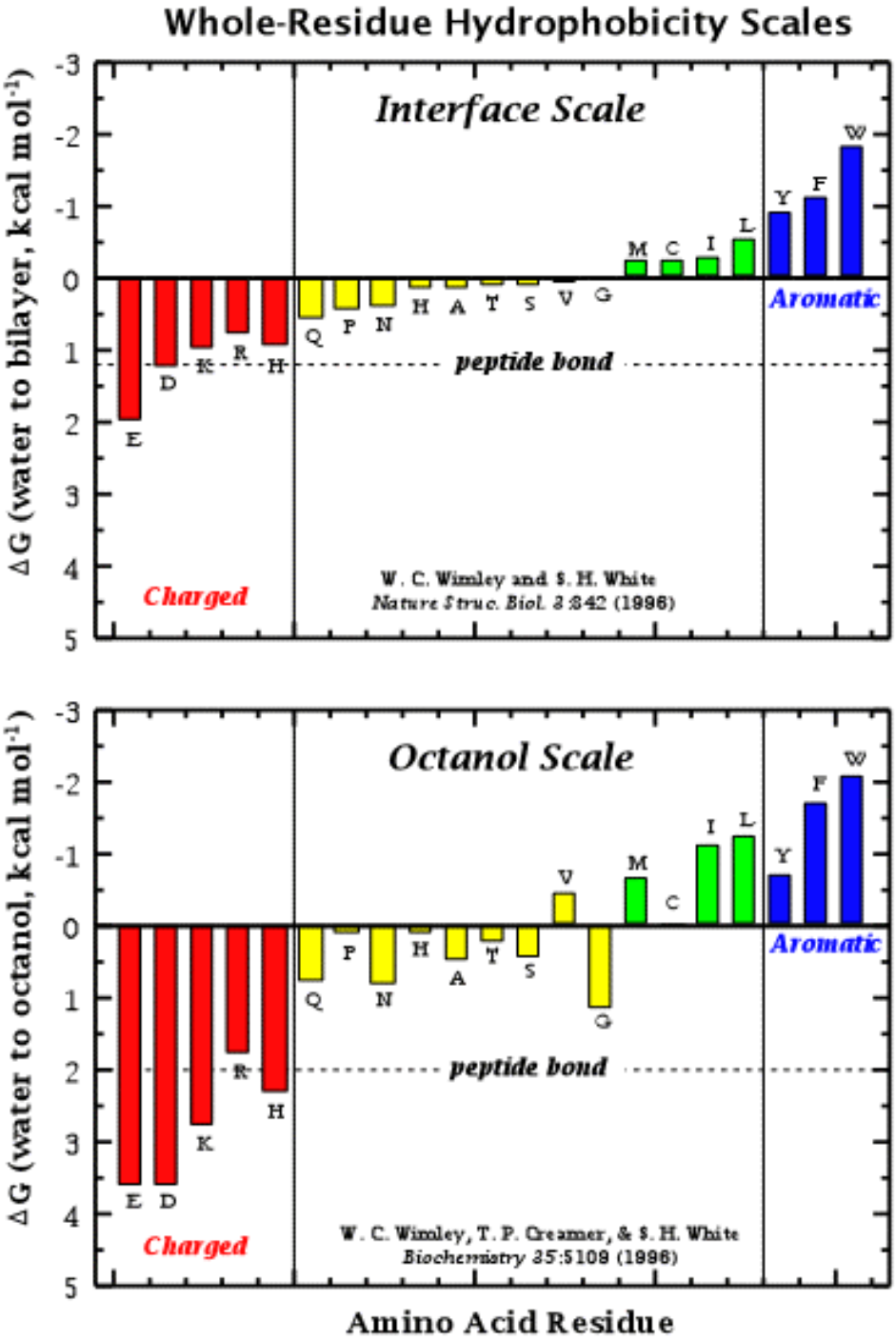
Citation

Algorithm Citation:

Kyte J., Doolittle R.F. "A simple method for displaying the hydropathic character of a protein.", J. Mol. Biol. 157:105-132(1982).

W.R. Pearson & D.J. Lipman PNAS (1988) 85:2444-2448.

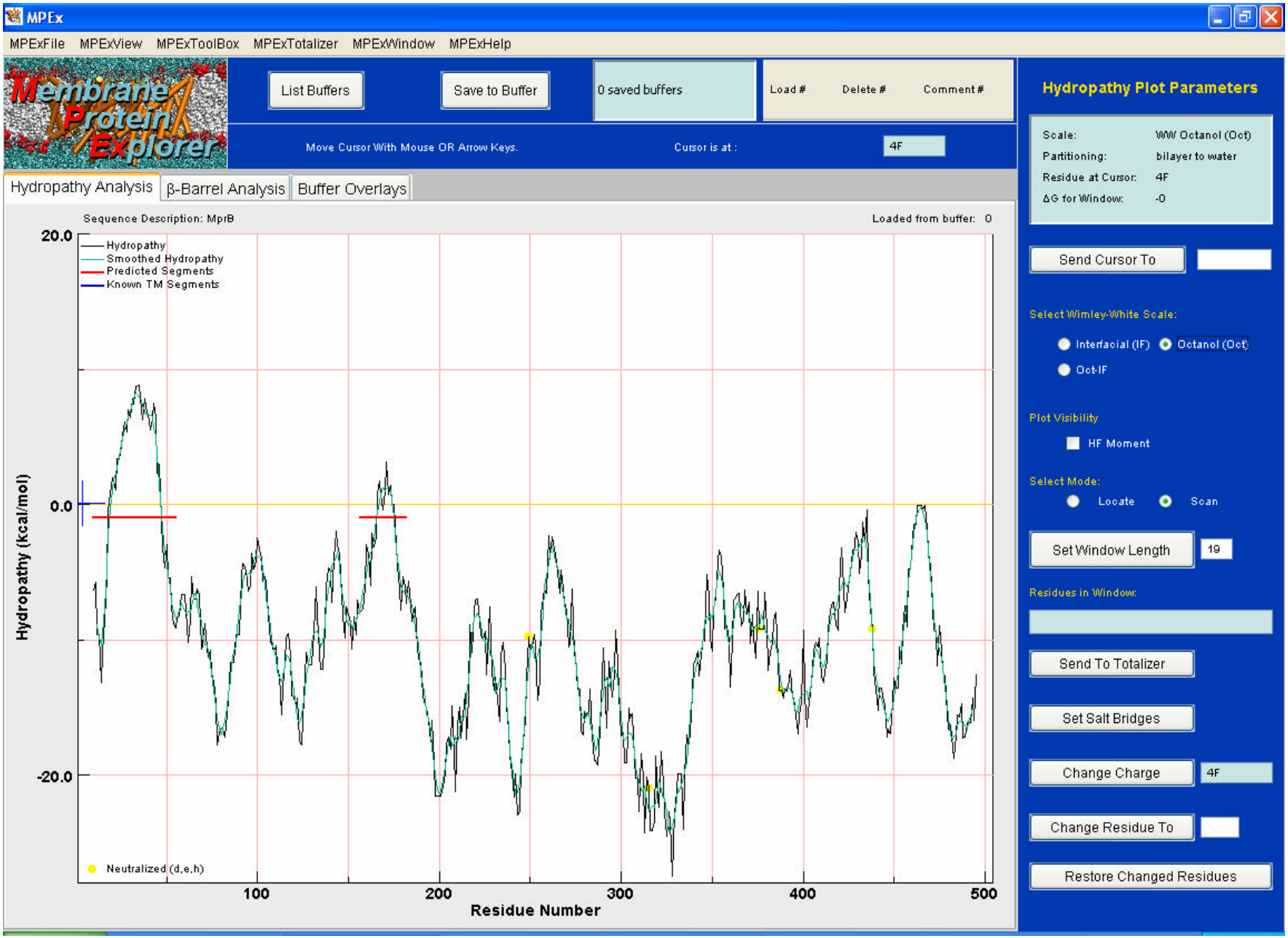
http://workbench.sdsc.edu



Wimley-White hydrophobicity scales: Thermodynamic, based on free energy of partitioning for "host-guest" peptides (e.g., Ac-KWLLxLL)

Octanol:water scale – better predictor of TM helices

Interface scale – more useful for peptide partitioning



MprB, using octanol scale

http://blanco.biomol.uci.edu/mpex/

MprB, using interface scale

http://blanco.biomol.uci.edu/mpex/

MPEx data output files for MprB

Hydropathy analysis results for protein: MprB

All Asp charged: true
All Glu charged: true
All His neutral: true

Changed residues: None
Scale: WW Octanol (Oct)

Window: 19
Mode: Locate
Partitioning: bilayer to water

Number of hydropathy predicted segments: 2
26,55: LLAMSMVAMVVVLMSFAVYAVISAALYSDI
DG = 8.73 for most favorable 19AA centered at #35V
(LLAMSMVAMVVVLMSFAVY)

162,180: LRWVLLIVGGIGVAVAAVA
DG = 3.12 for most favorable 19AA centered at #171G
(LRWVLLIVGGIGVAVAAVA)

Hydropathy analysis results for protein: MprB

All Asp charged: true
All Glu charged: true
All His neutral: true

Changed residues: None
Scale: WW Interfacial (IF)

Window: 19
Mode: Locate
Partitioning: bilayer to water

Number of hydropathy predicted segments: 4
34,52: MVVVLMSFAVYAVISAALY
DG = 3.61 for most favorable 19AA centered at #43V
(MVVVLMSFAVYAVISAALY)

164,182: WVLLIVGGIGVAVAAVAGG
DG = 2.51 for most favorable 19AA centered at #173G
(WVLLIVGGIGVAVAAVAGG)

345,363: IGWQVYGDTAGLSRMALNL
DG = 1.26 for most favorable 19AA centered at #354A
(IGWQVYGDTAGLSRMALNL)

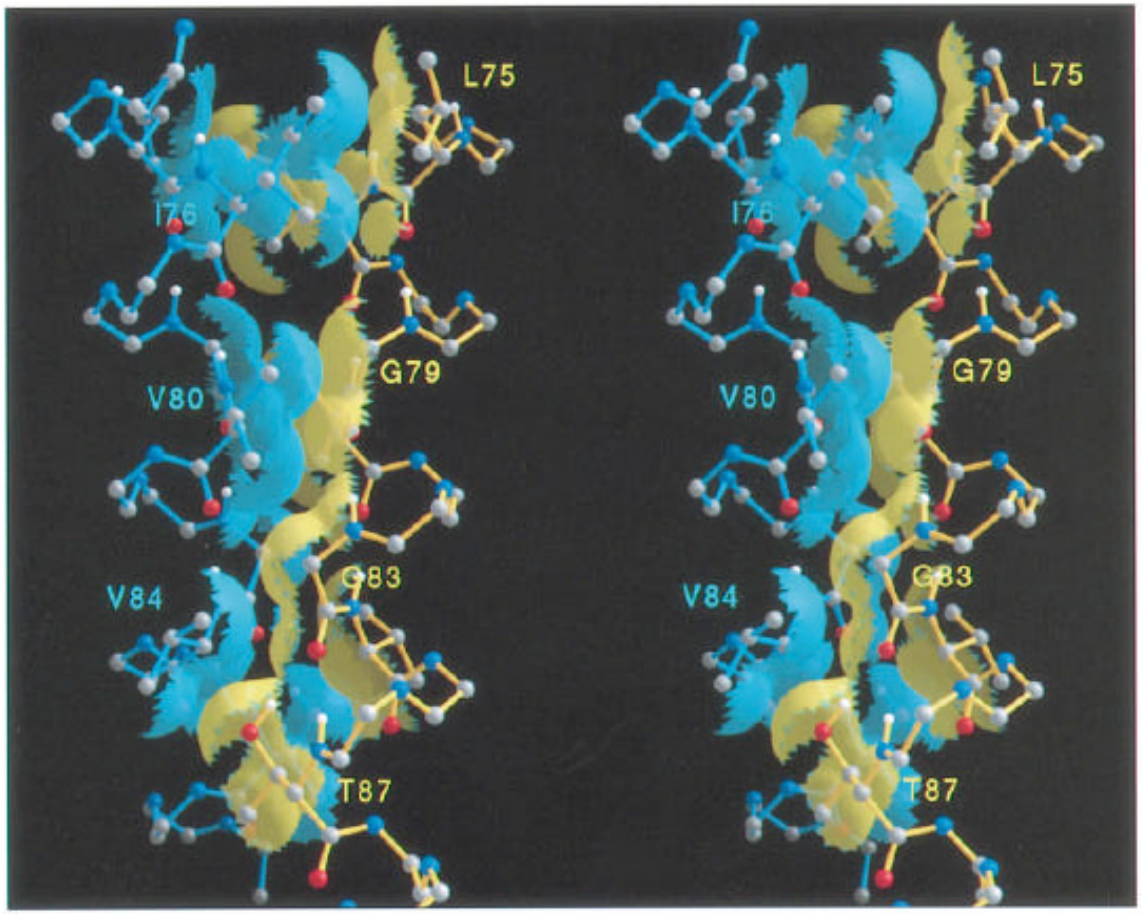
412,442: FYRSASARALPGSGLGLAIVKQVVLNhGGLL
DG = 0.89 for most favorable 19AA centered at #421L
(FYRSASARALPGSGLGLAI)

Helix – Helix Interactions

- What are the forces governing interactions between TM a-helices?

- How specific are those interactions?

Helix-helix interactions in glycophorin A



Glycophorin A – single TM helix. Forms SDS-stable dimers

Mutagenesis studies → a critical role for glycine residues 79 and 83

NMR structure → van der Waals interactions only, no interhelical H-bonds

"knobs into holes" alignment of Val with Gly

MacKenzie et al., Science 276, 131 (1997)

The TOXCAT assay

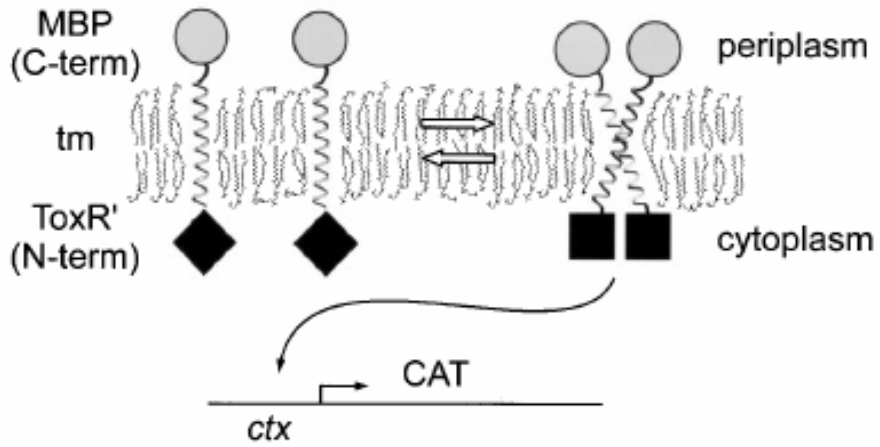


Figure 1. The TOXCAT assay for transmembrane domain oligomerization. Transmembrane (tm) helix-helix association mediates the activation of chloramphenicol acetyltransferase (CAT) from the *ctx* promoter by dimerized ToxR cytoplasmic domains (ToxR′, squares). The C-terminal, periplasmic maltose-binding protein (MBP, circles) domain anchors the chimera in the *E. coli* inner membrane.

(a)

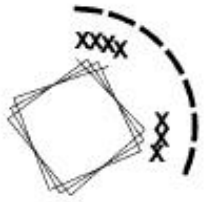
1 2 5 6 9 10 13

...nlgnrAS **X X** A A **X X** A A **X X** A A **X** AILInpsqs...

...nlgnrAS **X X** L L **X X** L L **X X** L L **X** LILInpsqs...

X = G, A, V, L, I, S, T, P, R

(b)



X positions varied randomly → library clones surviving in Cam sequenced

Russ and Engleman
J. Mol. Biol. (2000) 296, 911-919

The GxxxG motif

Table 1. Sequences of library isolates

LEULIB

GVLLGVLLGLLLGL	GVLLGLLLGVLLTL	GPLLGGLLGGLLAL	SLLLGVLLGLLLAL
AGLLGALLGSLLTL	VLLLGVLLGVLLTL	VGLLGVLLGILLAL	VLLLGILLGVLLSL
LLLLGVLLGVLLAL	LVLLGILLGLLLAL	AVLLGVLLGSLLTL	GVLLGVLLGSLLTL
LILLGALLGGLLTL	ISLLSSLLSSLLTL	VLLLGGLLGALLTL	LVLLGVLLGLLLAL
LVLLGVLLGVLLTL	SVLLGVLLGVLLTL	LLLLGALLGALLTL	LLLLGVLLGALLTL
LSLLSGLLGSLLTL	SVLLGLLLGALLTL	TILLGVLLGSLLTL	LLLLGGLLGALLTL
SILLGILLGILLTL	VLLLGVLLGVLLAL	GVLLGVLLGSLLTL	LVLLGVLLGALLTL
SLLLGVLLGLLLAL	LVLLGVLLGLLLAL	PLLLGVLLGILLTL	VLLLGILLGVLLSL
PLLLGLLLGLLLGL	ALLLGVLLGVLLAL	PGLLGLLLGALLGL	TLLLGALLGVLLTL
TVLLGVLLGLLLTL	LVLLGVLLGVLLSL	GILLGILLGILLTL	LVLLGALLGILLTL
GLLLGILLGLLLGL	SLLLGILLGLLLGL	LVLLGALLGSLLTL	LLLLGGLLGALLTL
SLLLGVLLGVLLTL	GVLLGILLGVLLTL	LLLLGVLLGLLLGL	LVLLGALLGALLTL
			LVLLGVLLGLLLGL

ALALIB

ISAAAGAALGAAIA	IGAALGAAVGAAIA	ISAAVGAALGAAVA	SGAASGAAIGAALA
PAAAIGAAIGAAVA	PSAAAGAAIGAALA	GSAAIGAAIGAAVA	AGAAAGAAIGAALA
TSAAISAAVSAAVA	GGAAVGAALGAAIA	VAAAAGAAVGAALA	SSAAAGAALGAAVA
LSAAVGAALGAAAA	PGAAVSAALGAAIA	TGAAIGAALGAAIA	SSAAIGAAVGAAIA
LGAAAGAAIGAAVA	PGAALGAAVGAAIA	GGAALGAALGAAVA	PVAAALAAGIAAGA
SSAASGAAVAAAIA	GPAAVGAALGAAVA	GSAALGAAIGAAVA	LGAALGAAVGAAVA
SSAAIGAALGAAVA	LSAAIGAAVGAAAA	IGAAAGAAIGAAVA	GSAAVGAALGAAVA
GAAAIGAALGAAVA	LGAAIGAAVGAAVA	SSAAVGAAIGAAVA	VGAALGAAIGAAIA
PGAALGAALGAAVA	LSAALGAAIGAAIA	LPAALGAAIGAALA	LVAAISAAVGAAVA
LGAAVGAAVGAAVA	LAAAVGAAIGAAIA	IGAALGAAIGAAVA	PTAAIGAAVGAAIA
SSAALGAAIGAAVA	LSAASGAAIGAAIA	VGAAVGAAIGAATA	PGAAVSAALGAAIA
LSAALGAALGAAVA	IGAAVGAAIGAAAA	ISAALGAALGAAVA	GGAAGIAAVSAALA
SSAAVGAALGAAVA	GGAAVGAALGAAIA	GTAAVGAALGAAIA	GGAATSAAIGAAIA
GAAAIGAAIGAAVA	AGAAIGAAVGAAVA	VVAAISAAVSAAVA	PGAAIGAAVGAAVA
LLAAGVAAGVAAGA	GAAALGAAVGAAIA	SSAAISAALGAAIA	TSAAISAAVSAAVA
LGAAAGAAIGAAVA	GGAAIGAAIGAAVA	SGAATGAALGAALA	LGAAIGAAVGAALA
GSAATGAALGAAIA	TTAASLAAPLAAIA	LPAAAGAAVGAALA	GGAAVGAAVGAAVA
PGAAIGAALGAAIA	GAAAVGAAIGAAVA	GIAASSAAIGAAVA	SIAAVSAALGAALA

Table 2. Comparison of sequence motifs with sequences from the SwissProt database

Pattern from library[a]	Matches in homology cleared SwissProt[b]	Related patterns in SwissProt[c]
LEULIB		
GxxxG	1641	GxxxG
GxxxGxxxT	68	GxxxGxxxT
G[Sm]xxG[Sm]xxT	5	[GAS]xxx[GAS] G[GAS]xxG GxxxG[GAS]
G[Lg]xxG[Lg]xx[Sm]	78	[VLI]xxx[VLI] G[VLI]xxG GxxxG[VLI]
ALALIB		
GxxxG	1641	GxxxG
[Lg]Gxx[Lg]Gxx[VI]	80	[VLI]Gxx[VLI] [VLI]xxx[VLI]G [VLI]GxxxG Gxx[VLI]G

[a] [Sm] indicates residues with small side-chains (Gly, Ala, Ser). [Lg] indicates residues with large side-chains (Val, Leu, Ile). Positions involved in the pattern are shown as capitals, intervening positions are labeled x.

[b] The number of times each motif appears in a homology-cleared database of 13,606 sequences derived from SwissProt (Senes *et al.*, 2000).

[c] Related two- and three-residue sequence patterns identified by Senes *et al.* (2000) to occur in transmembrane domains from the SwissProt database much more frequently than expected.

Functional classes of membrane proteins

- Receptors – ligand-induced conformational change initiates signaling through a second messenger system
- Channels – ligand, pressure or voltage-induced conformational change opens a permeation pathway
- Transporters – transfer substrates across the membrane coupled to an energy source

Channels

- Transmembrane proteins that provide hydrophilic pores across the lipid bilayer
- Allow diffusion of solutes down a concentration gradient
- General types
  - Ligand gated
  - Voltage gated
  - Mechanosensitive
  - Diffusion

Mechanosensitive channels

- Widely distributed across all kingdoms
- Ion channels that open in response to sound, pressure → hearing, touch in mammals
- Non-specific channels that protect prokaryotic cells from osmotic stress:

  Normally, high concentration of osmolytes in the bacterial cytoplasm → driving force for water transport into cell → turgor pressure of cytoplasmic membrane against cell wall (essential for bacterial gowth).

  A sudden decrease in extracellular osmolarity → rapid uptake of water → cell lysis.

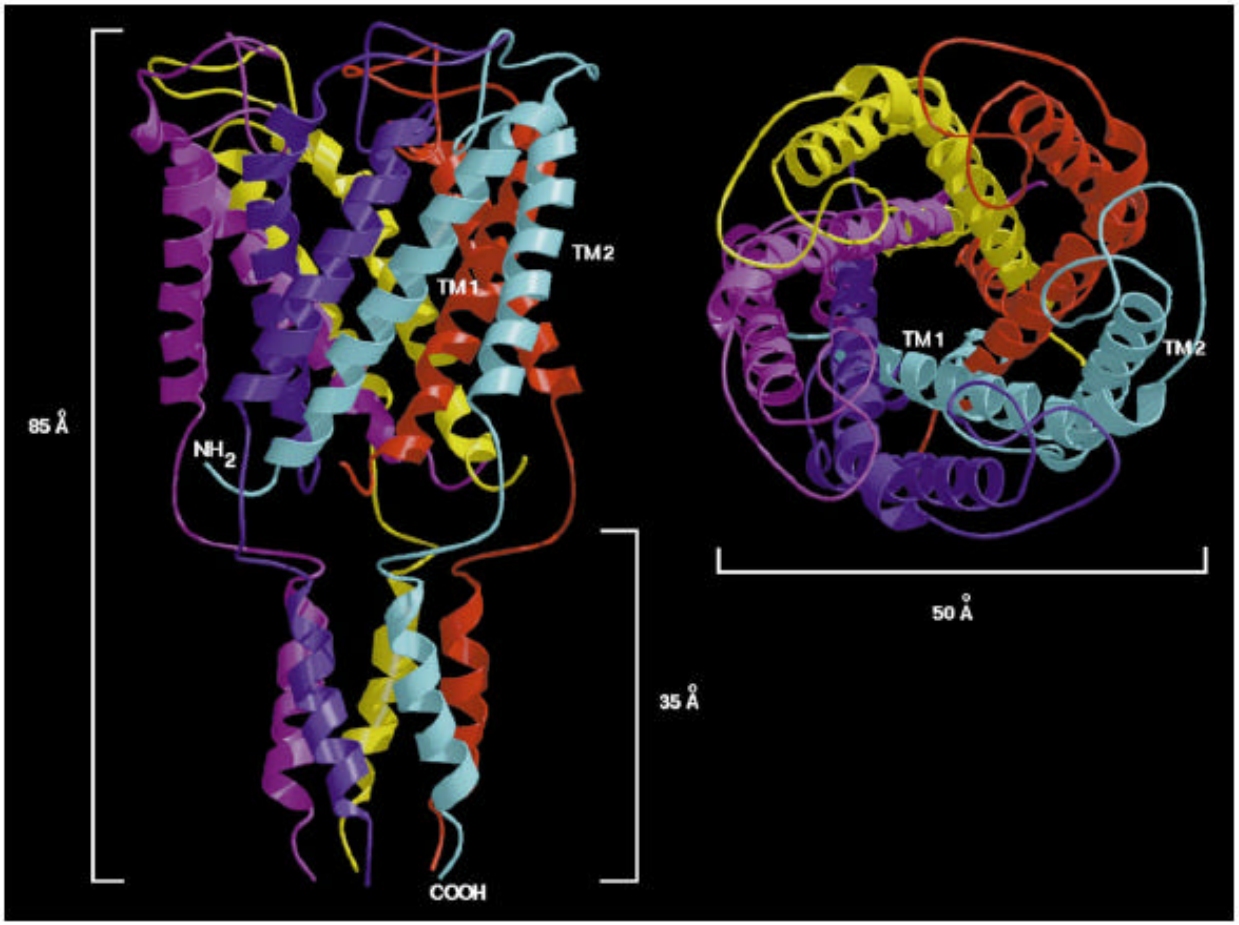
  To prevent lysis, mechanosensitive channels open, allowing ions and other osmolytes to flow out of the cell and maintain osmotic balance.

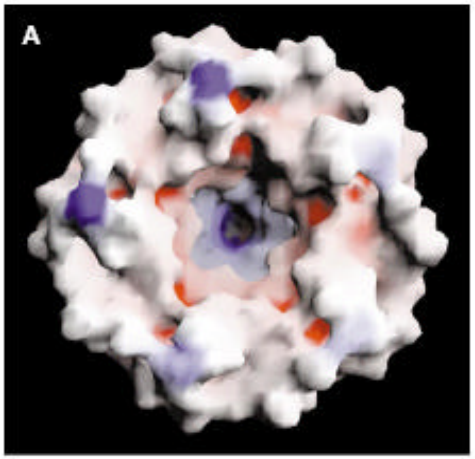
Bacterial mechanosensitive channels

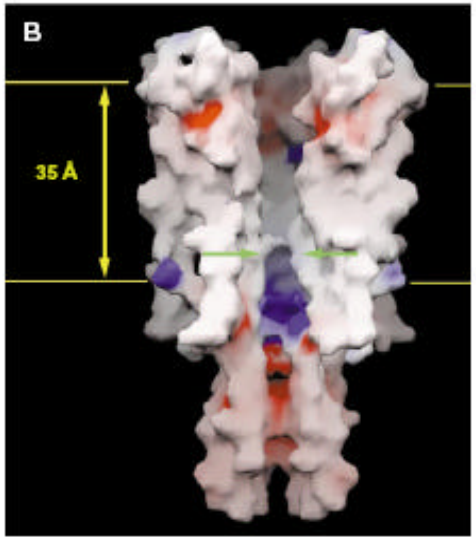
- MscL (mechanosensitive channel of large conductance)
  - Symmetric homopentamer
  - Opens at near the rupture threshold

- MscS (mechanosensitive channel of small conductance)
  - Symmetric homoheptamer
  - Opens at ~ 50% pressure required to open MscL (i.e., opens first)
  - Also opens in response to membrane depolarization

MscL from M. tuberculosis (putative closed state)



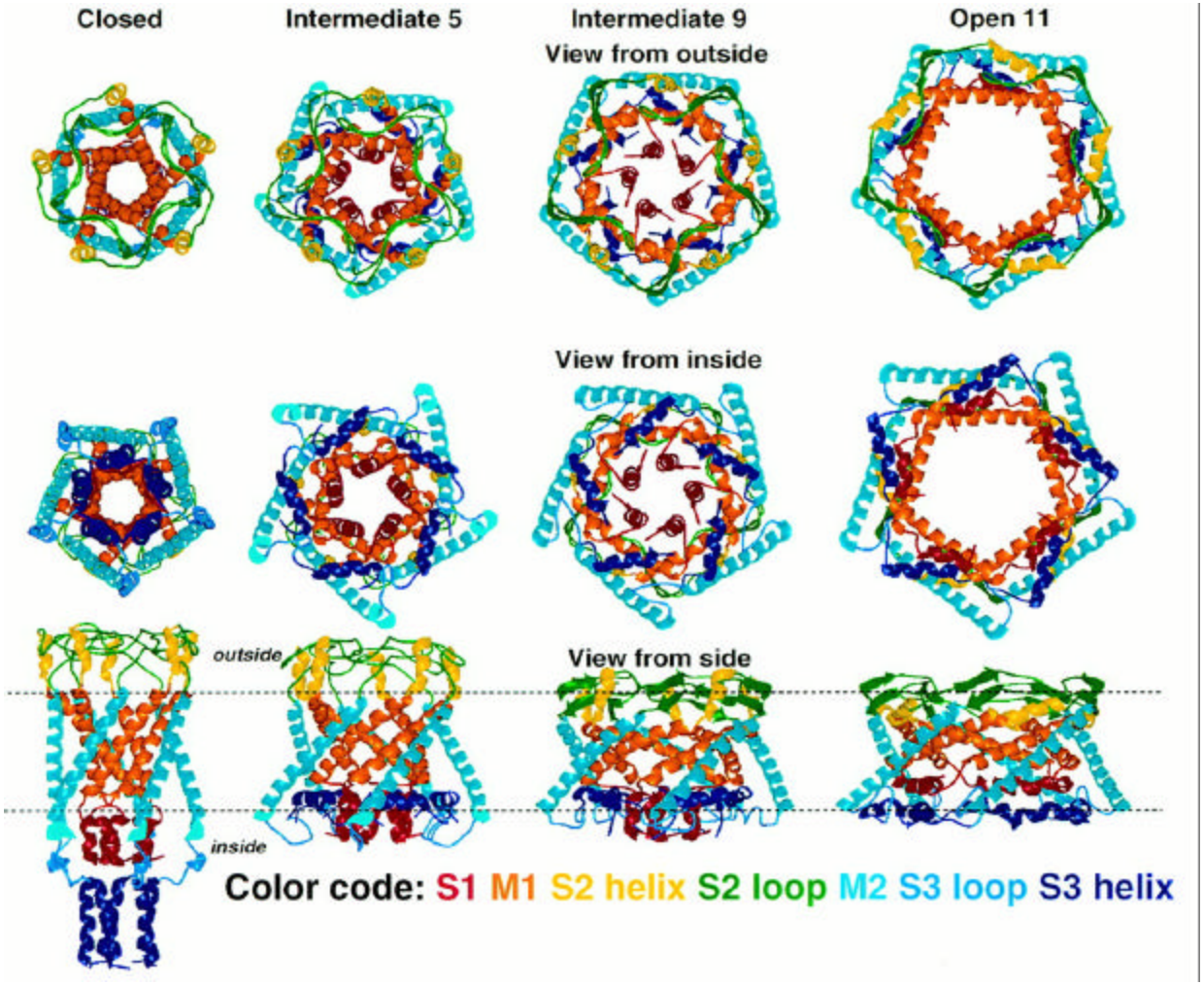




- pentamer
- twoTM helices per subunit
- pore diameter varies 2 – 18 Å

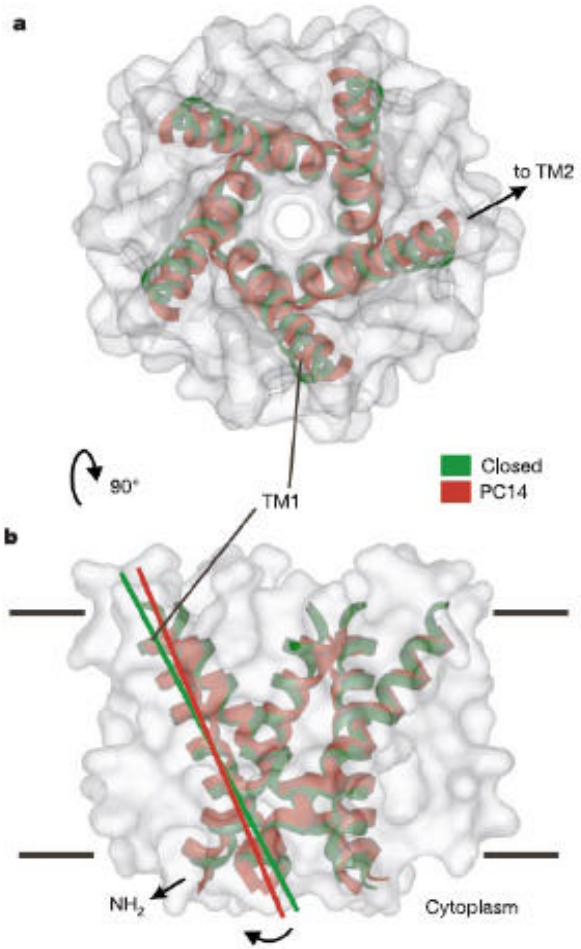
Chang et al., Science 282, 2220 (1998)

Model of MscL channel opening :
rigid-body sliding and tilting of transmembrane helices

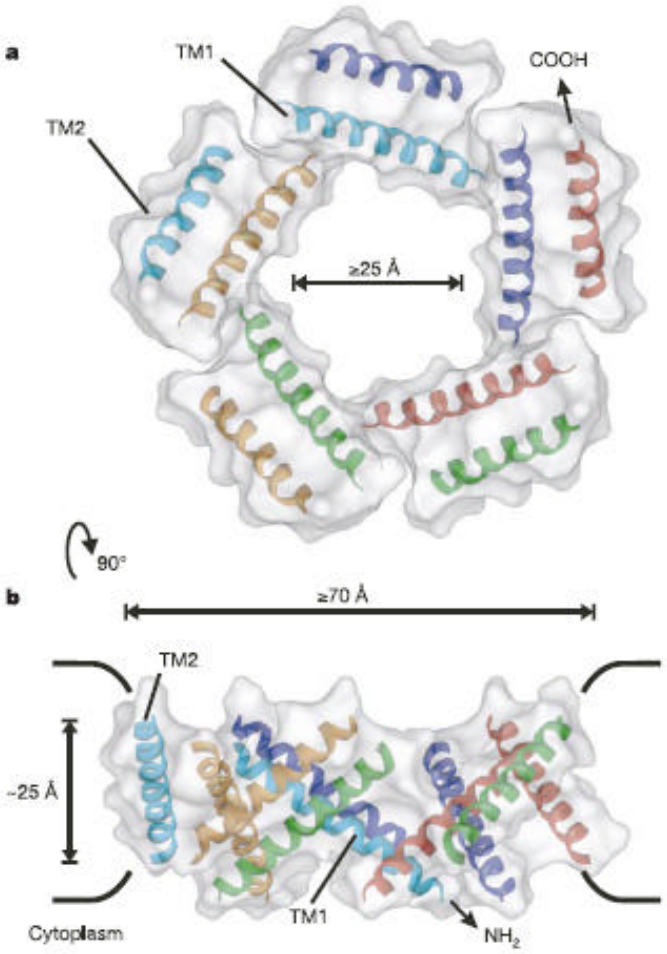


Sukharev et al.,Biophys J, 81, 917-936, (2001)

Gating mechanism of MscL from spin labeling



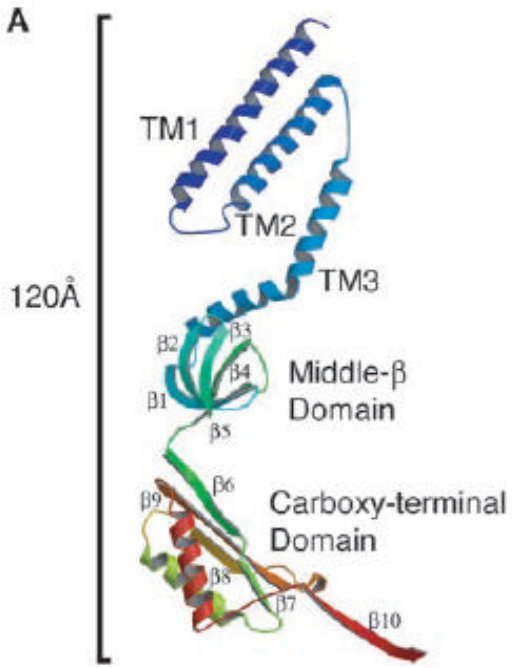
Closed

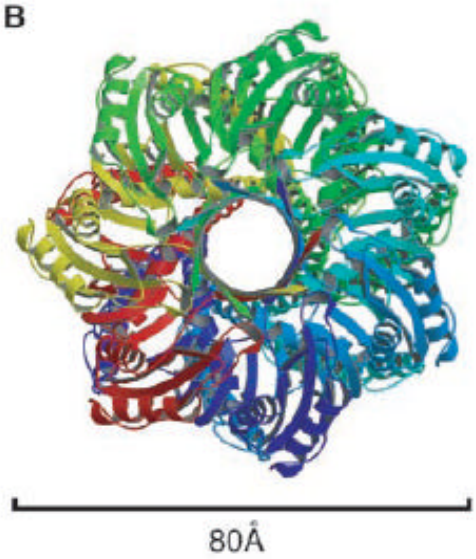


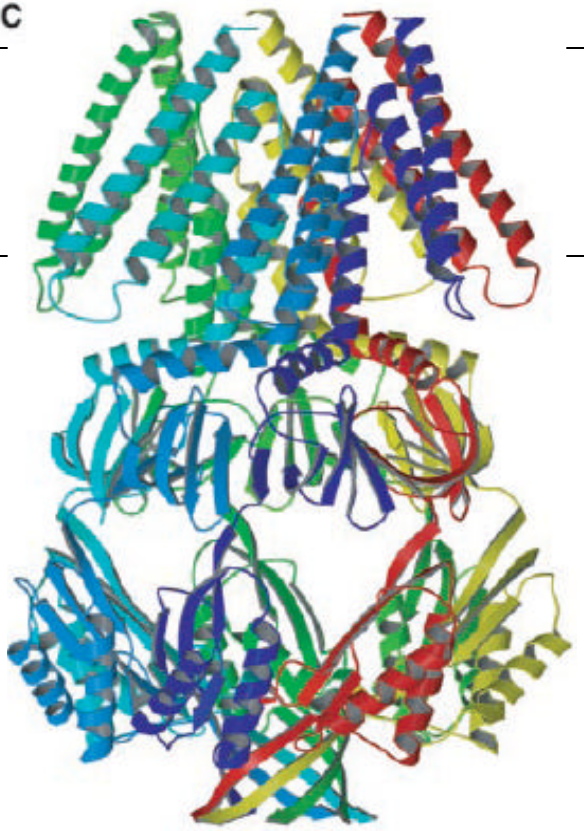
Open

Perozo et al., Nature 418, 942 (2002)

MscS (open state)



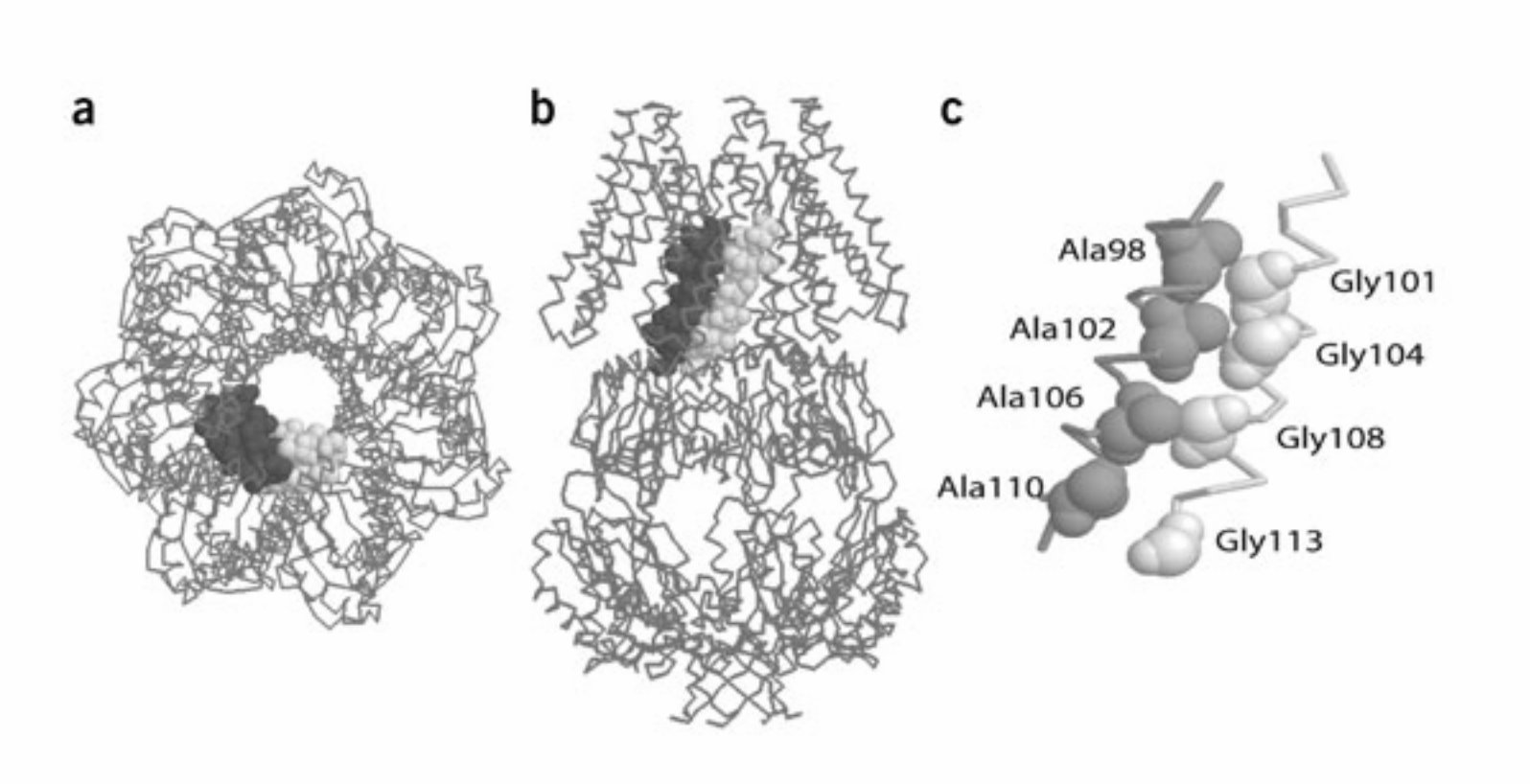




- heptamer
- three TM helices per subunit
- pore diameter ~ 11 Å

Bass et al., Science 298, 1582 (2002).

Mechanism of MscS channel gating



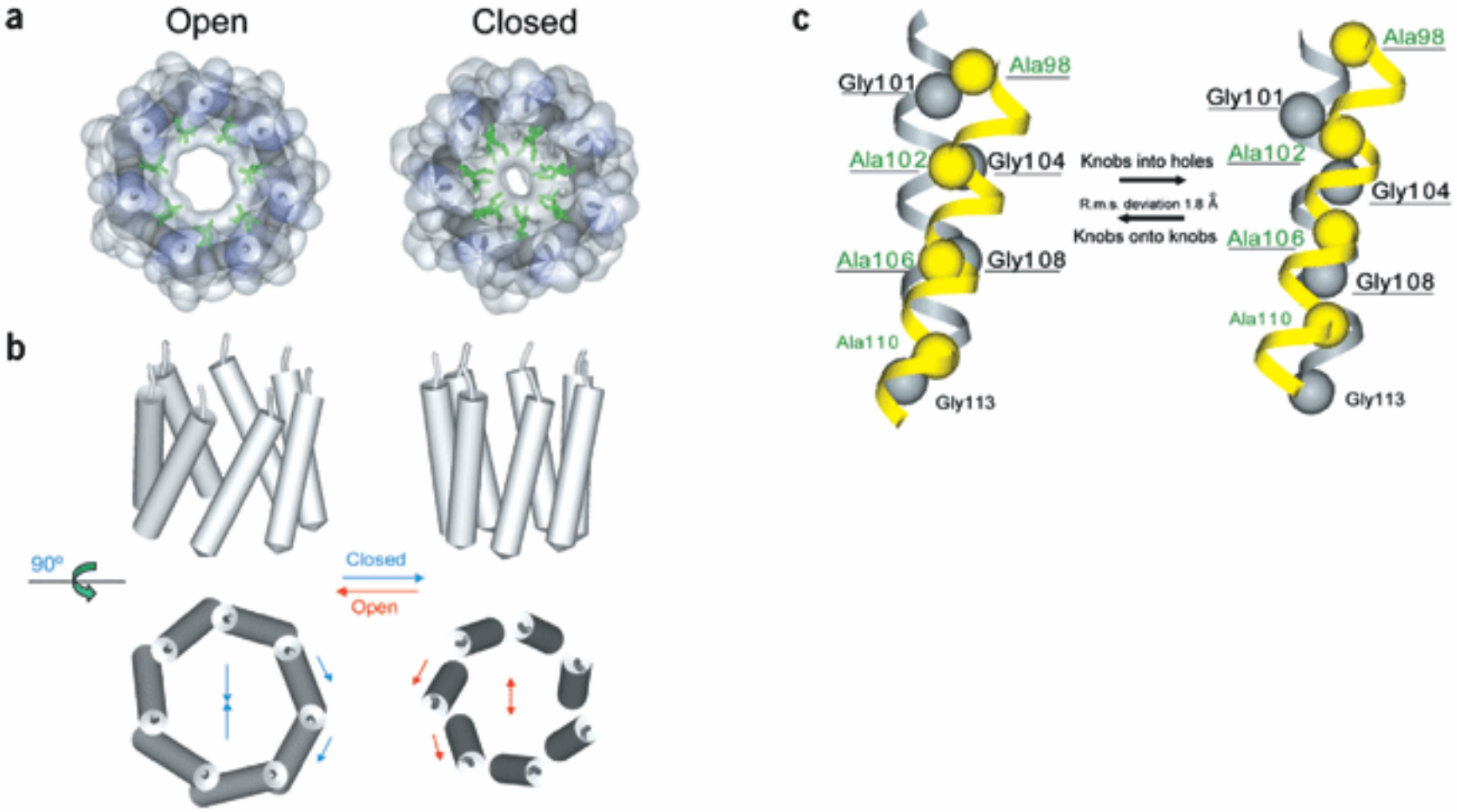
- Conserved pattern in TM3: AxxGAxGxAxGxAxxG

- Adjacent helices exhibit “knobs into holes” packing

Edwards et al., Nature Struct. Biol. 12, 113 (2005)

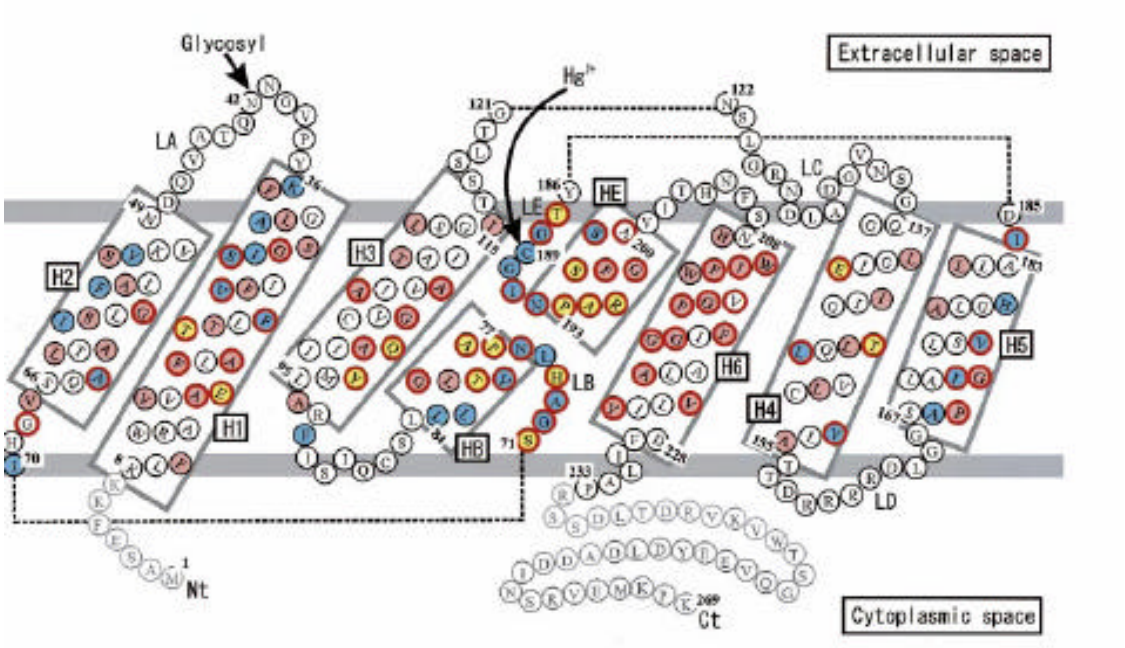
Model of MscS channel opening :

rigid-body sliding and tilting of transmembrane helices (again)



Aquaporin family of water channels

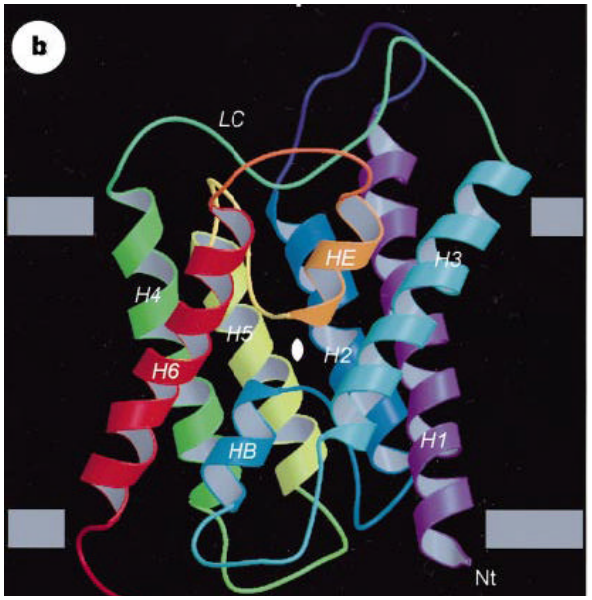
Found in yeast, bacteria, plants, and mammals (inclu. humans)
Over 150 known homologs
Arose through tandem intragenic duplication



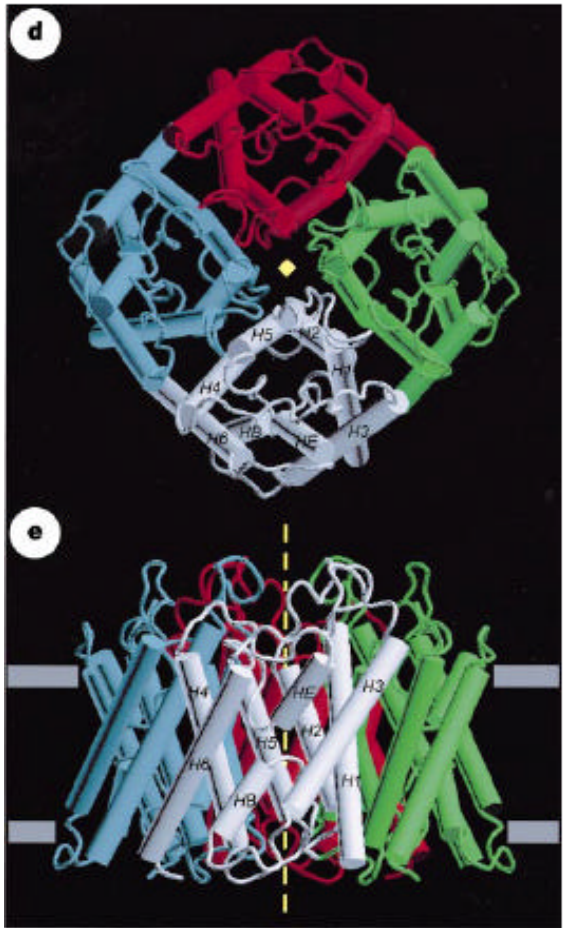
Mammalian aquaporin-1 channel

Two domains, each contributes 3 ½ helices
Conserved NPA motif at interface of half-helices

Aquaporin-1 (pdb 1FQY)



Monomer subunit



Tetramer

"Hourglass" structure

Pore diameter ~ 3 Å at constriction (water diameter 2.8 Å)

Each monomer contains a channel

Murata et al., Nature 407, 599 (2000)

Water transport through aquaporin-1

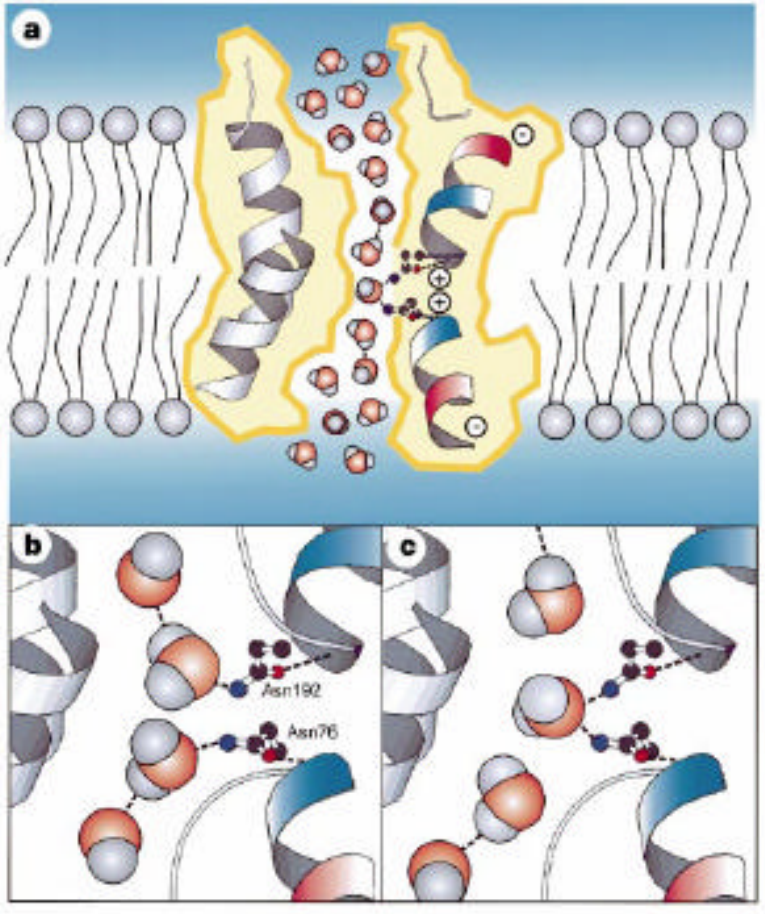
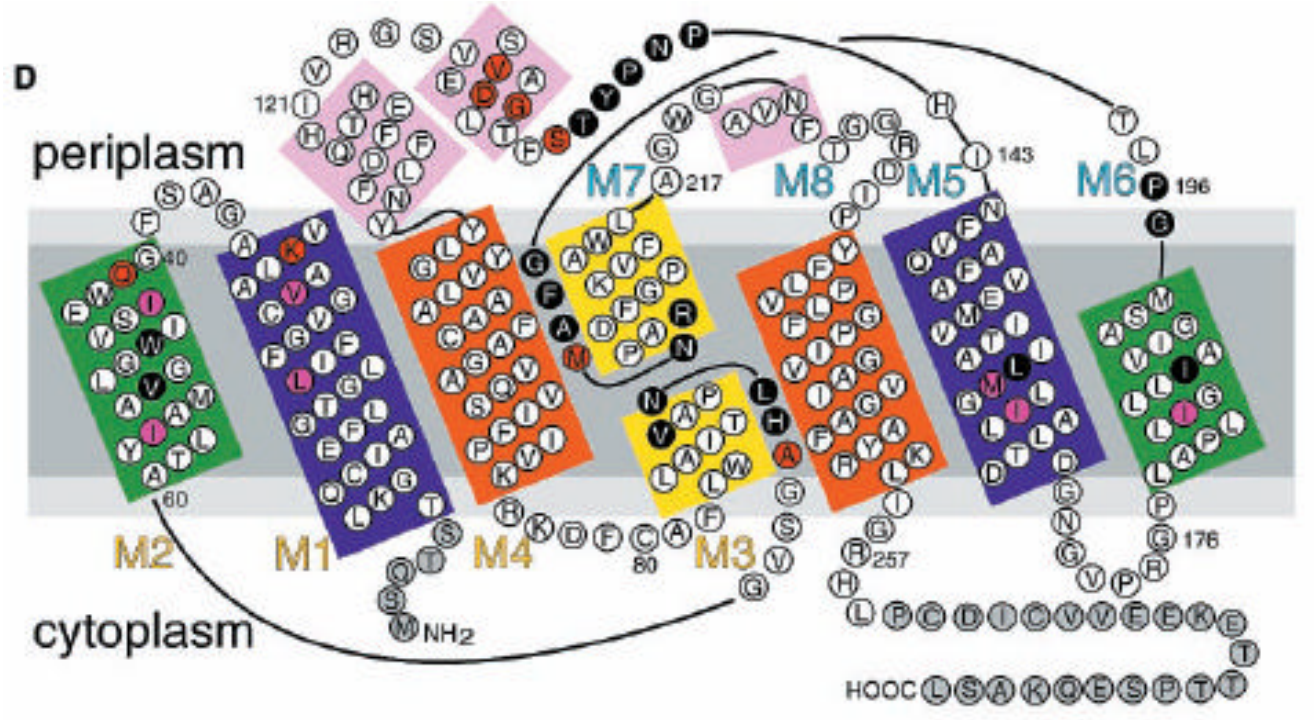


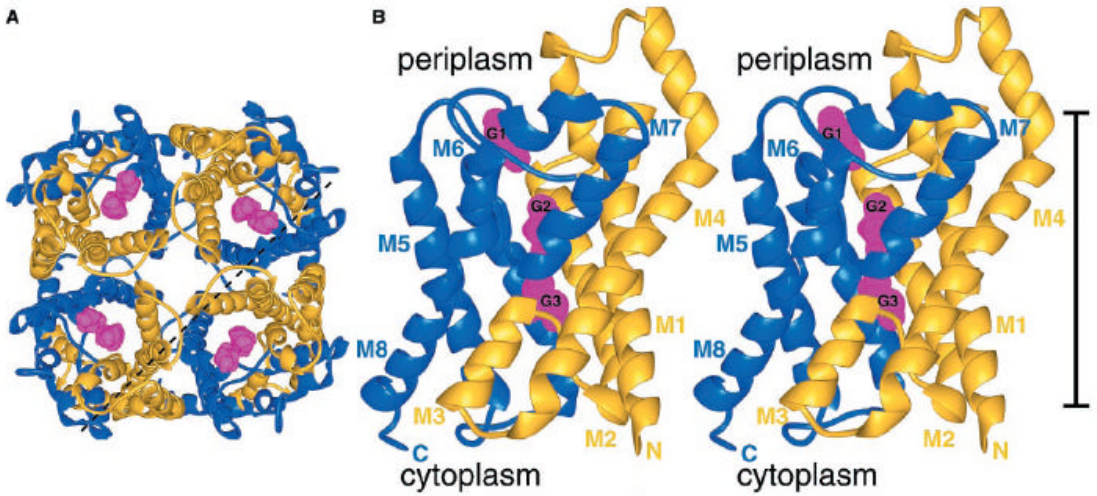
Figure (a) shows how helix dipoles restrict the orientation of water molecules passing through the constriction of the pore. (b and c) Hydrogen bonding of a water molecule with Asn 76 and/or Asn 192. In (c), both electron lone pairs of the water oxygen atom H-bond to Asn residues, breaking the chain that would otherwise allow H+ conduction.

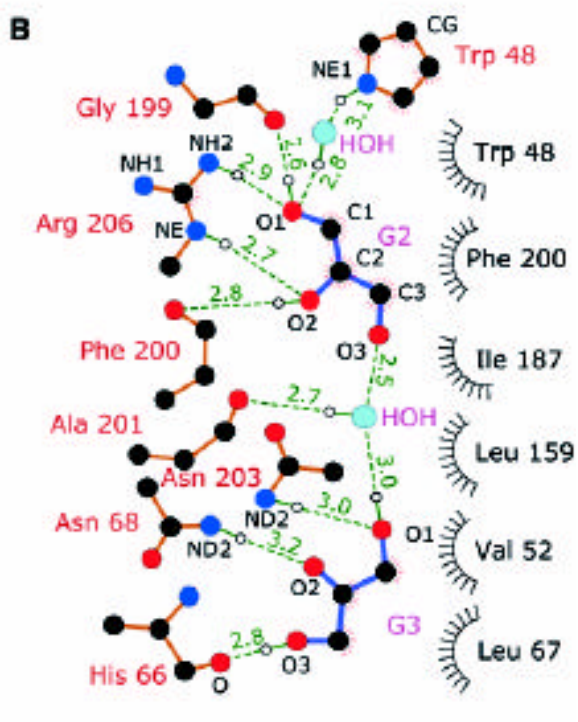
Membrane topography of the E. coli glycerol facilitator, GlpF



- Facilitates glycerol diffusion by factor of 100 – 1000x
- Conserved AQP structure, conserved NPA motif

GlpF glycerol channel (pdb 1FX8)





Conserved “hourglass” fold

Pore radius ~ 3.5 Å (too narrow for a hydrated ion (therefore impermeable to K^+, Na^+, or H^+)

One side of channel polar, the other hydrophobic (orients the glycerol)

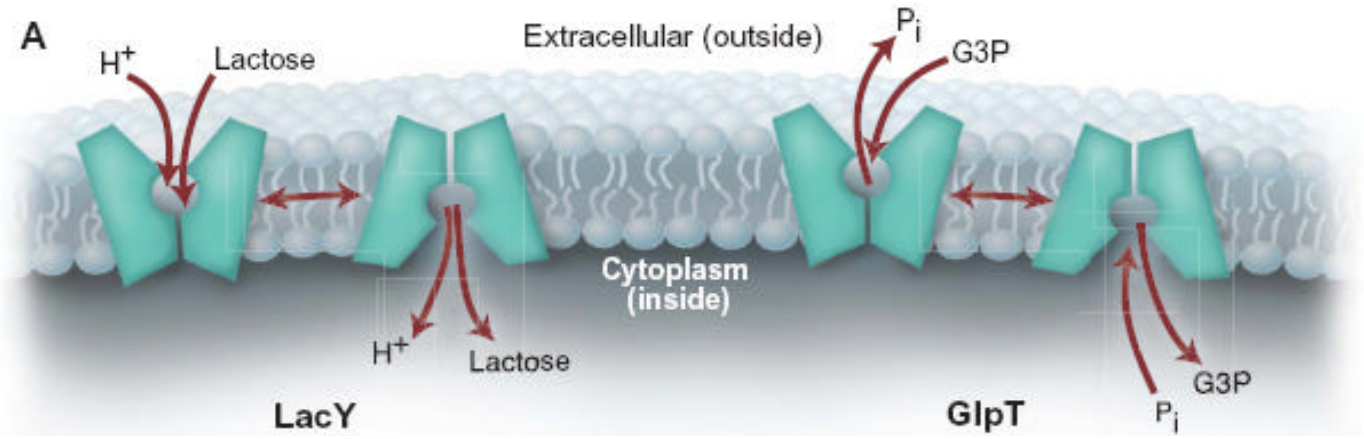
G3 bound to N68, N203 in the NPA motif

Fu et al., Science 290, 481 (2000)

Transporters

- Bind a specific substrate with high affinity
- Transport substrate *against* a concentration gradient by coupling to an energy source
  - ATP hydrolysis
  - Co-transport of a second substrate down its concentration gradient

Major Facilitator superfamily (MFS)

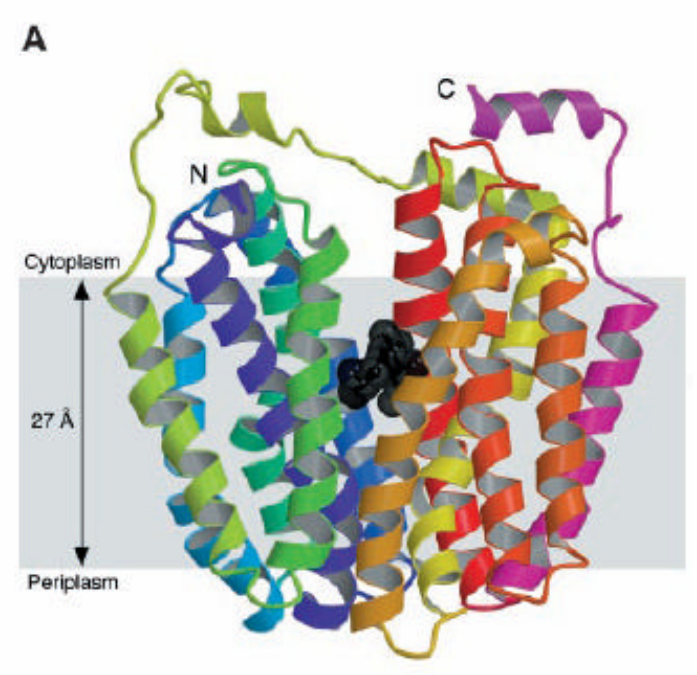


Alternating-access or "rocker" model of transport

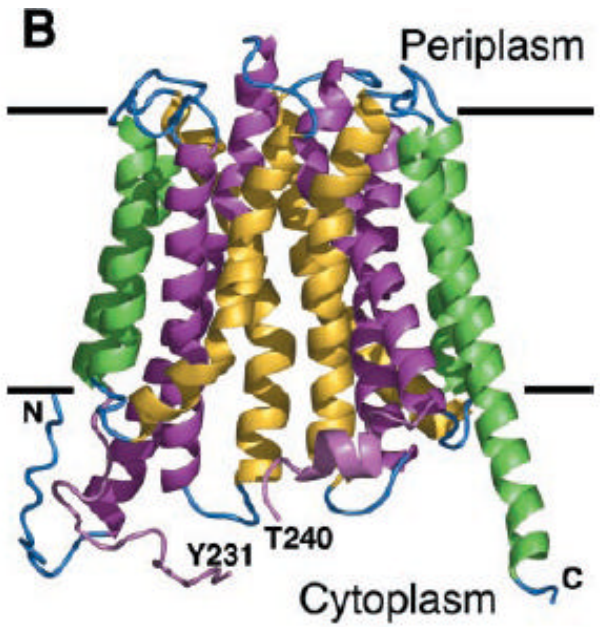
Transport of a substrate against a concentration gradient is coupled to transport of a second solute down its concentration gradient.

K. Locher, R. Bass, and D. C. Rees, Science 301, 603 (2003)

MFS transporter structure



LacY (lactose permease)

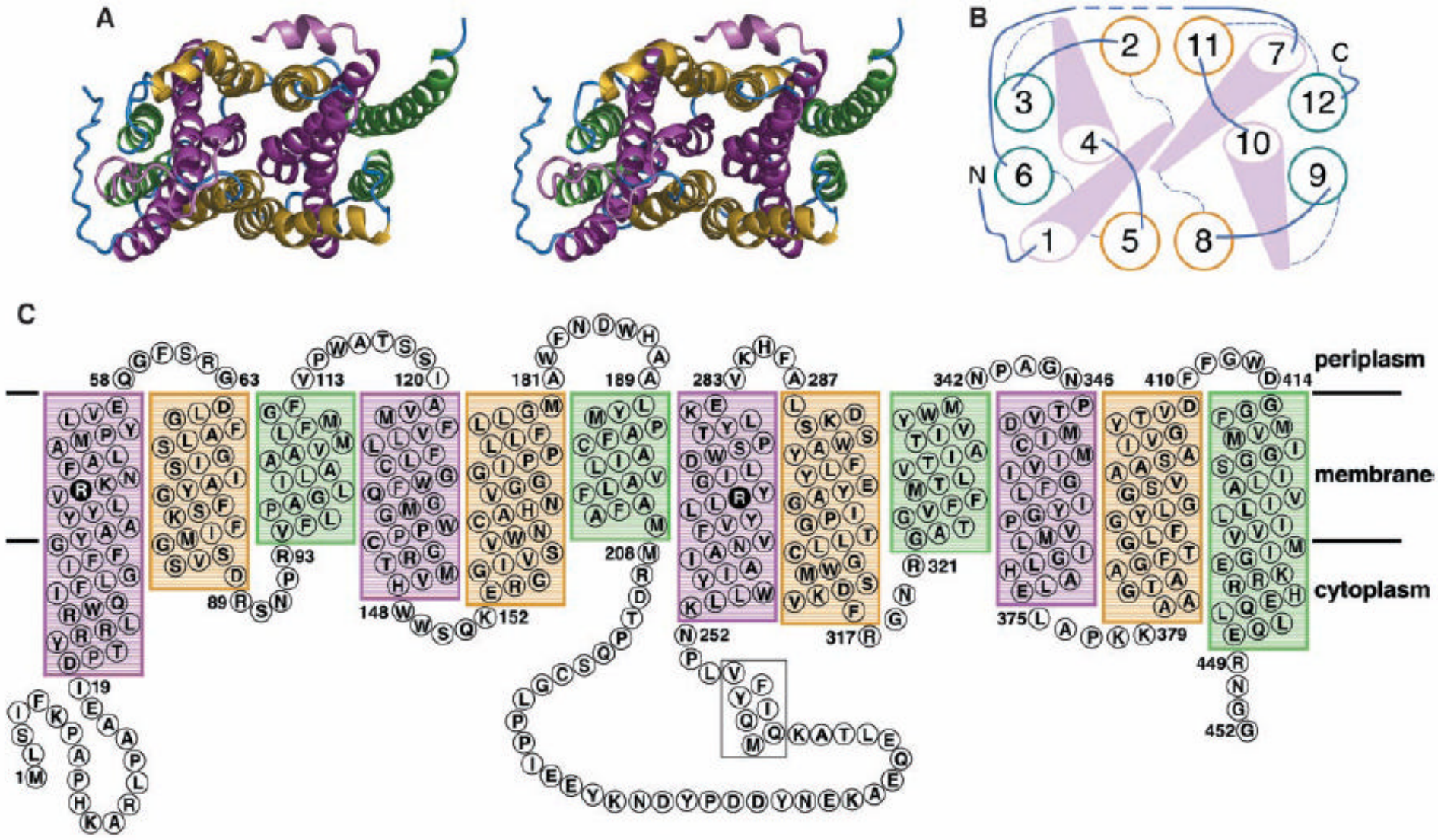


GlpT (glucose-3-PO_4)

- 12-transmembrane helices arranged in two distinct domains (six N-term helices and six C-term helices)

-Substrate binding site at the interface of N- and C-term domains

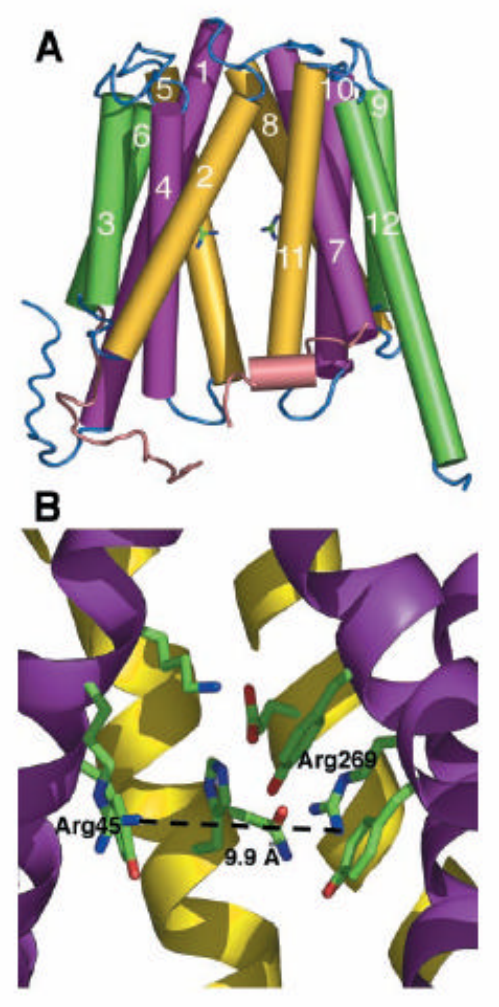
-Binding of substrate → conformational change

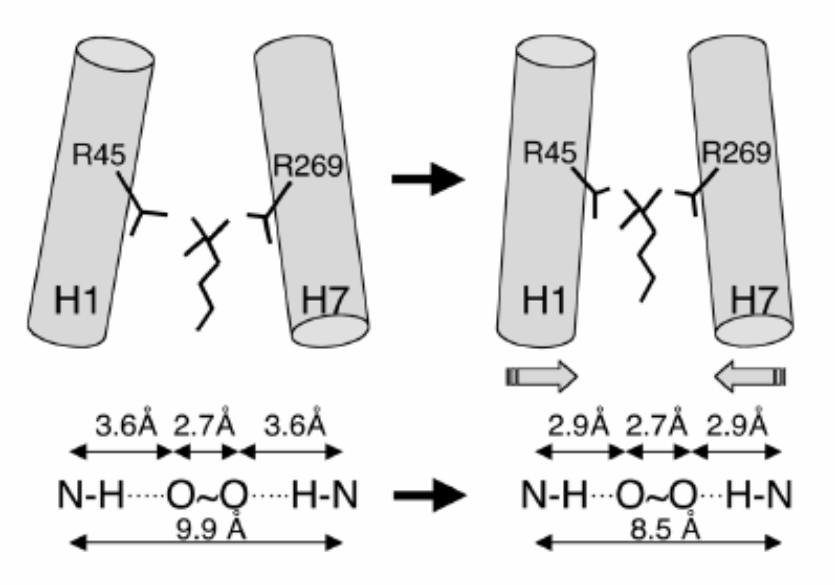


The E. coli glycerol-3-phosphate transporter, GlpT (1PW4)

Huang et al., Science 301, 616 (2003).

Mechanism of GlpT transport





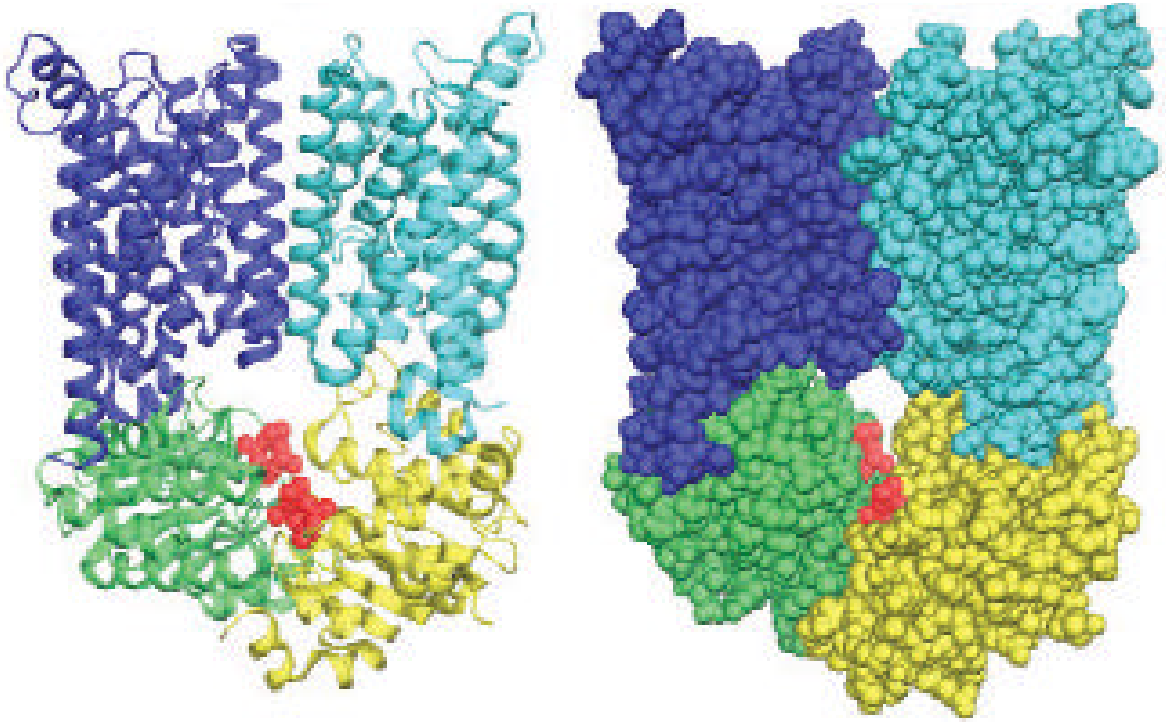
Binding of substrate causes a rigid-body movement of helices H1 and H7, changing the conformational state of the protein.

Huang et al., Science 301, 616 (2003).

ATP-binding cassette (ABC) transporters

- Widely distributed across all species
- Transport a wide variety of substrates (Cl^- ions, antigenic peptides, essential nutrients, drugs)
- Responsible for multidrug resistance phenotype in both mammalian cells and bacteria
- Couple transport to ATP hydrolysis

ABC transporter structure

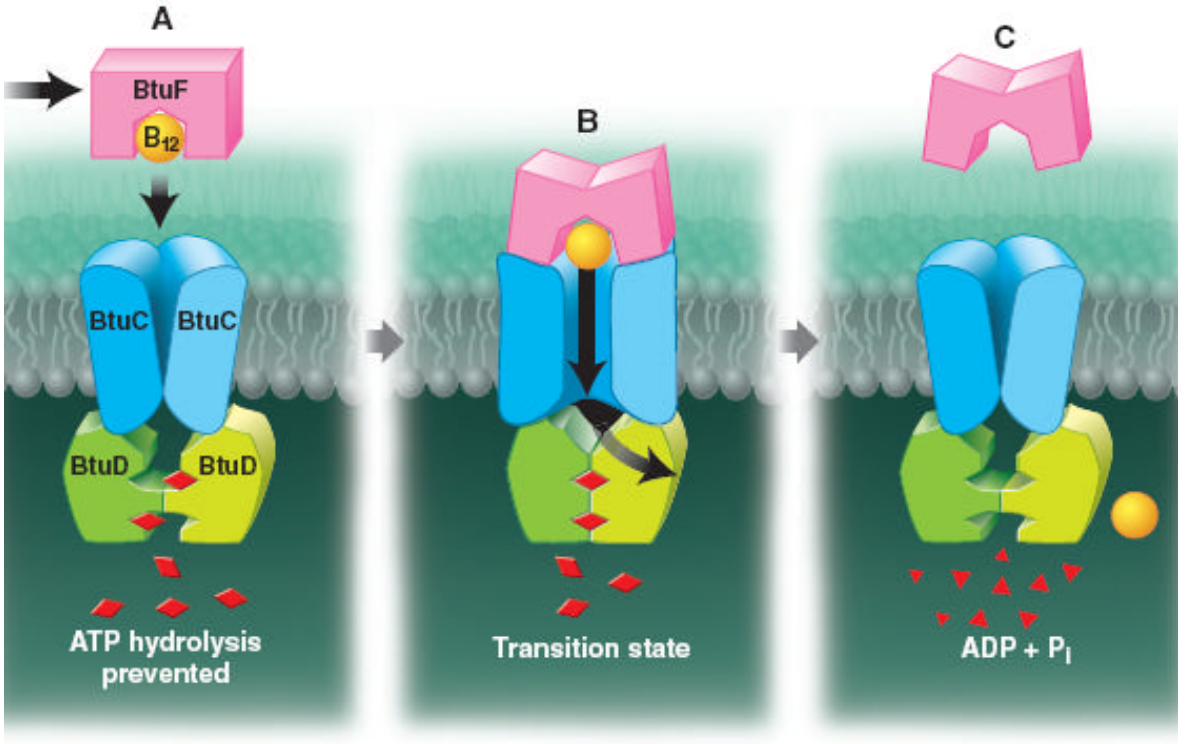


E. coli BtuCD

Locher et al., Science 296, 1091 (2002)

Two TM domains, each typically containing 6 TM helices
Two nucleotide binding domains (NBDs)
Two molecules of ATP bound at interface
Can be either single polypeptide or homodimer

Vitamin B12 uptake through BtuCD

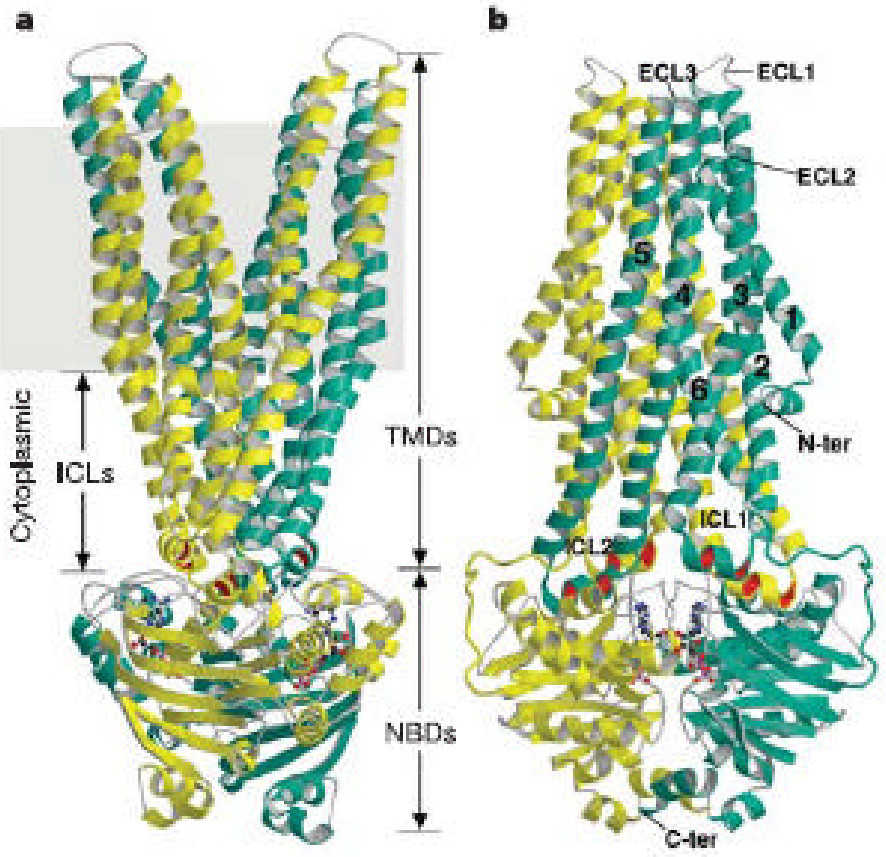


- NBDs and TM domains are separate gene products
- Substrate delivered from periplasm by specific binding protein

A. L. Davidson, Science 296, 1039 (2002)

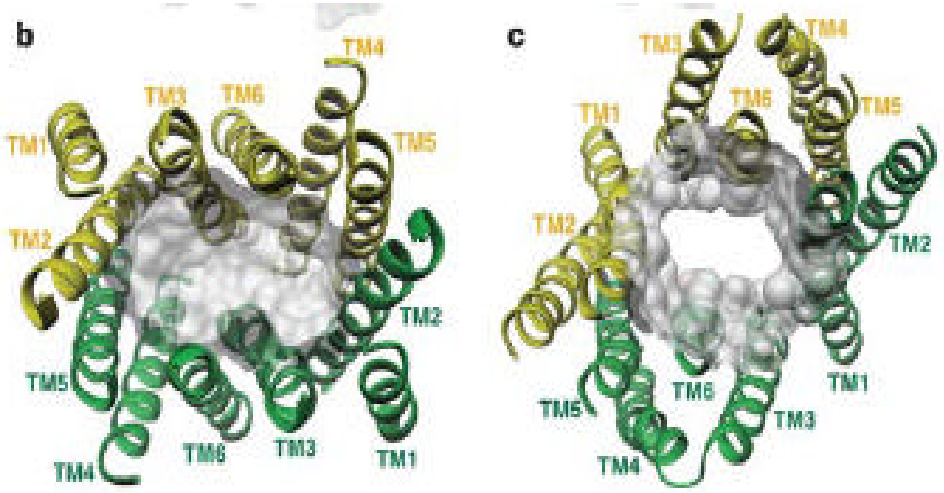
S. aureus Sav1866 multi-drug transporter

(crystallized in outward-facing conformation)

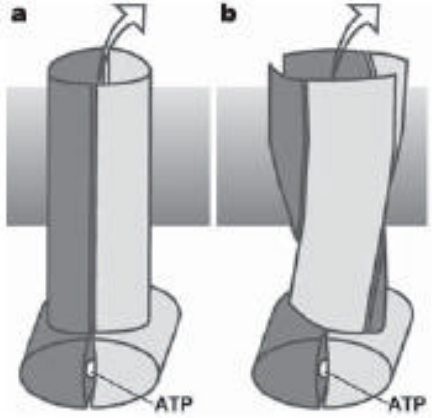


Dawson and Locher, Nature 443, 180 (2006)

Domain swapping in Sav1866



Arrangement of Sav1866 TM helices
(b) at level of inner (cytoplasmic) leaflet
(c) at level of outer (periplasmic) leaflet



ABC exporter schematics. a, Earlier cartoons depict two compact transporter halves (subunits) arranged side-by-side, suggesting separation during the transport cycle. The grey box indicates the location of the membrane. b, Schematic of Sav1866 in the observed, outward-facing conformation. The cartoon emphasizes the domain swapping and subunit twisting.

Dawson and Locher, Nature 443, 180 (2006)

Structural features of helical membrane proteins

- Close packing of transmembrane helices creates a sealed barrier that separates the hydrocarbon region of the lipid bilayer from the protein interior
- The α-helical secondary structure of TM helices satisfies all potential hydrogen bonding interactions along the peptide backbone
- The outer surface of TM helical bundles is > 95% nonpolar, and small side chains (especially glycine) are favored at helix-helix interfaces
- On average, TM helices are tilted ~ 20° from the membrane normal
- Rigid-body motions of TM helices (sliding, tilting, twisting) produce conformational changes that allow substrate transport/channel gating