

Prediction of membrane protein topology

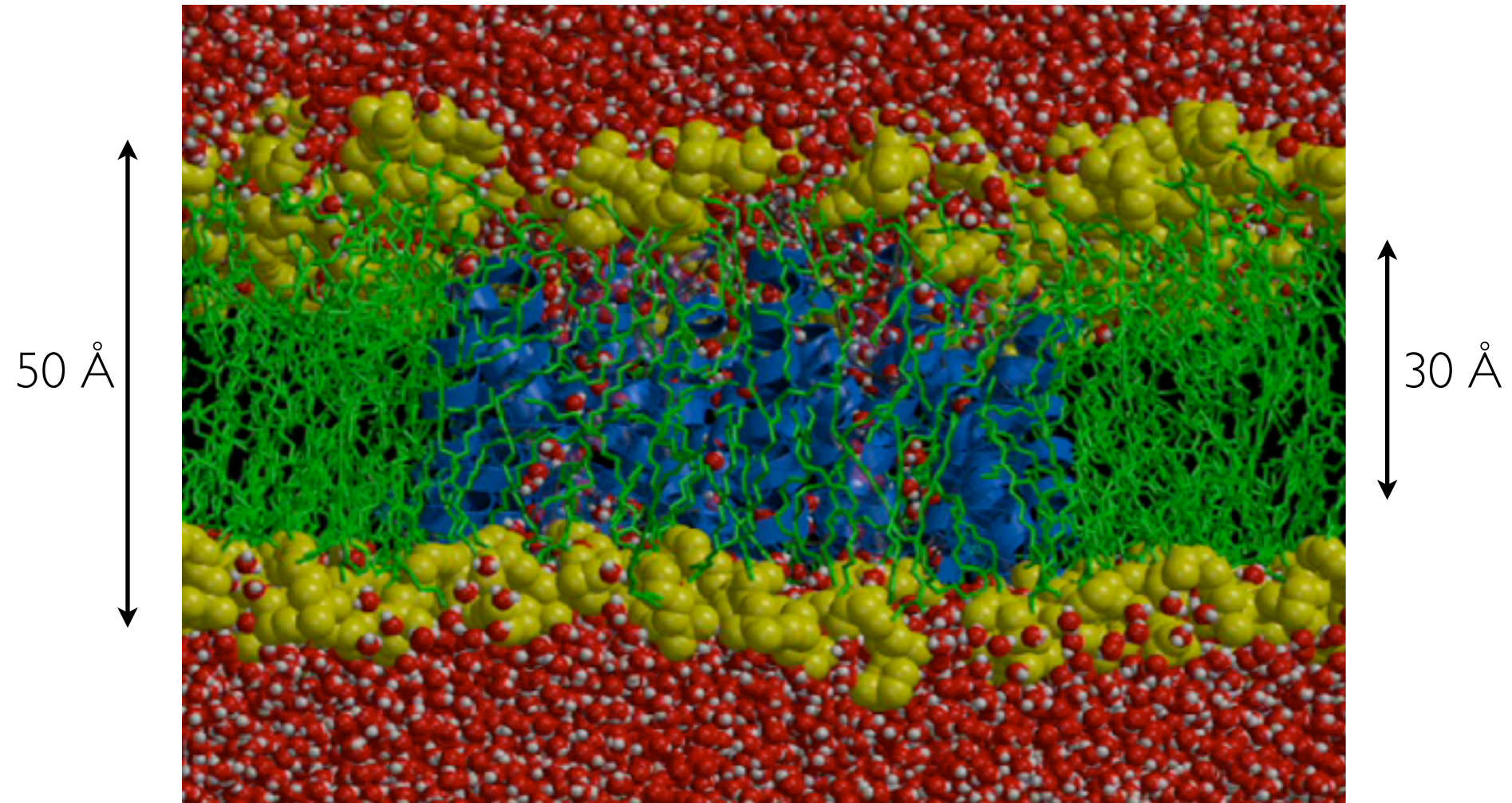
Gunnar von Heijne

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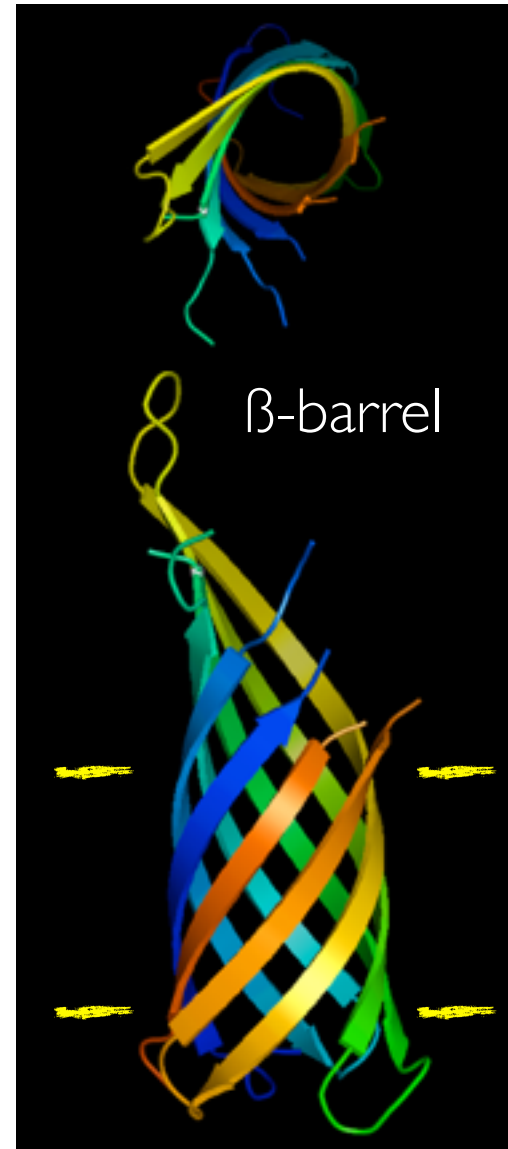
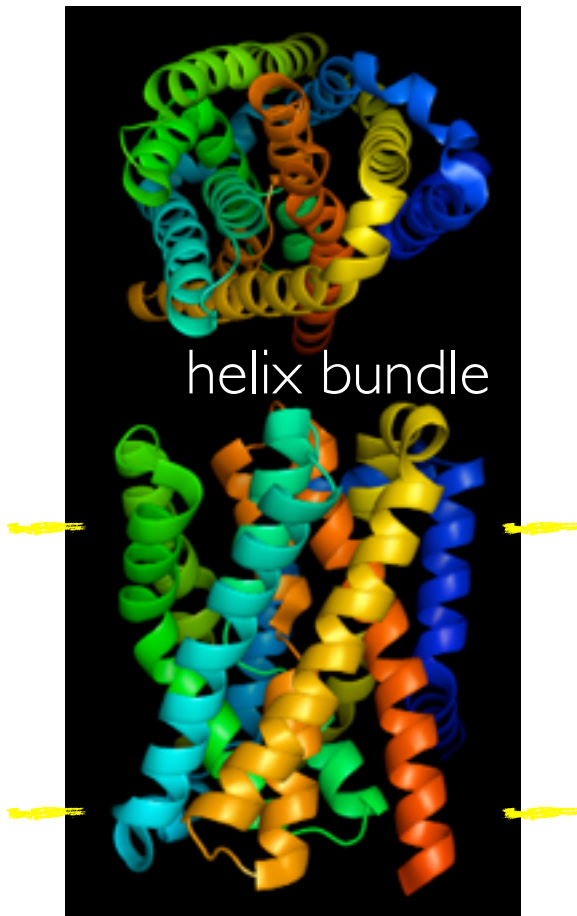


Center for Biomembrane Research

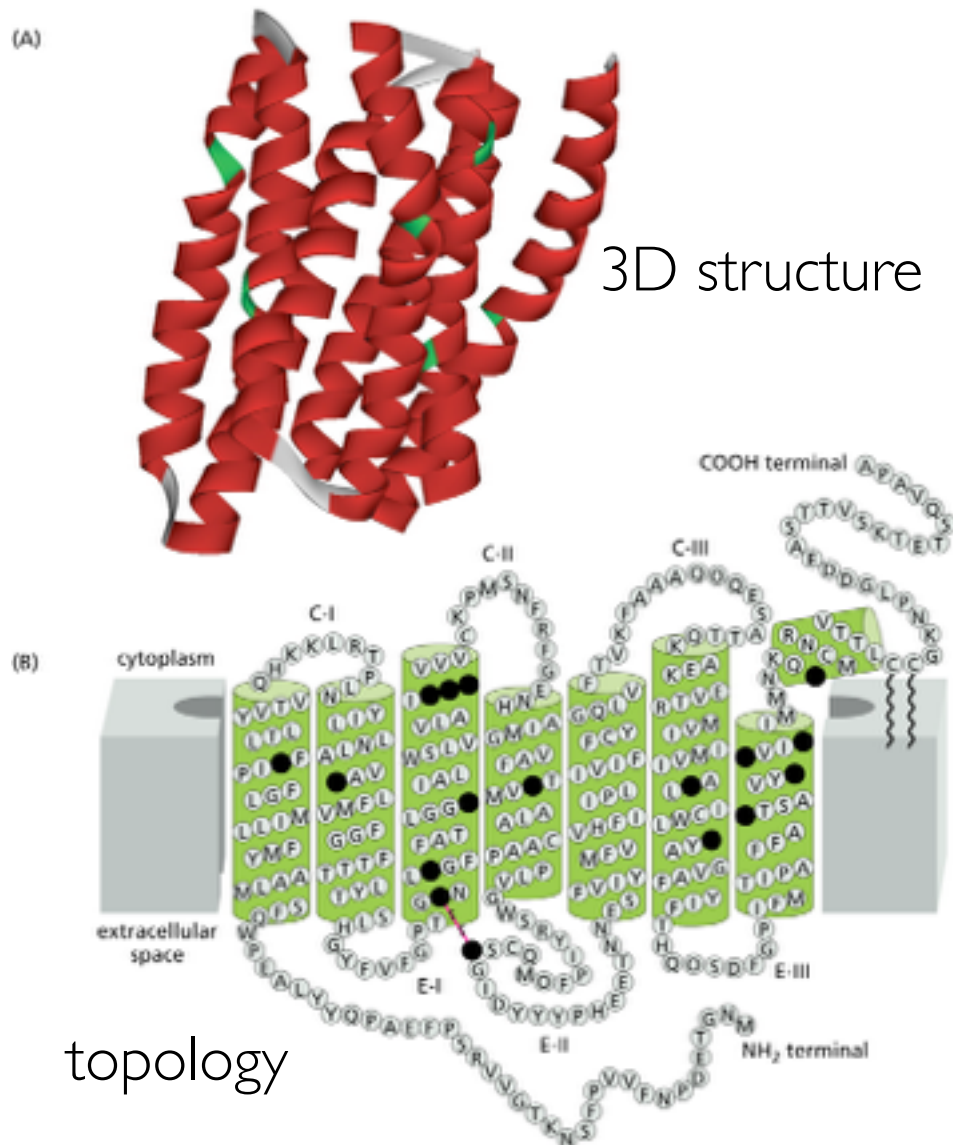
A simulated membrane



Only two basic architectures

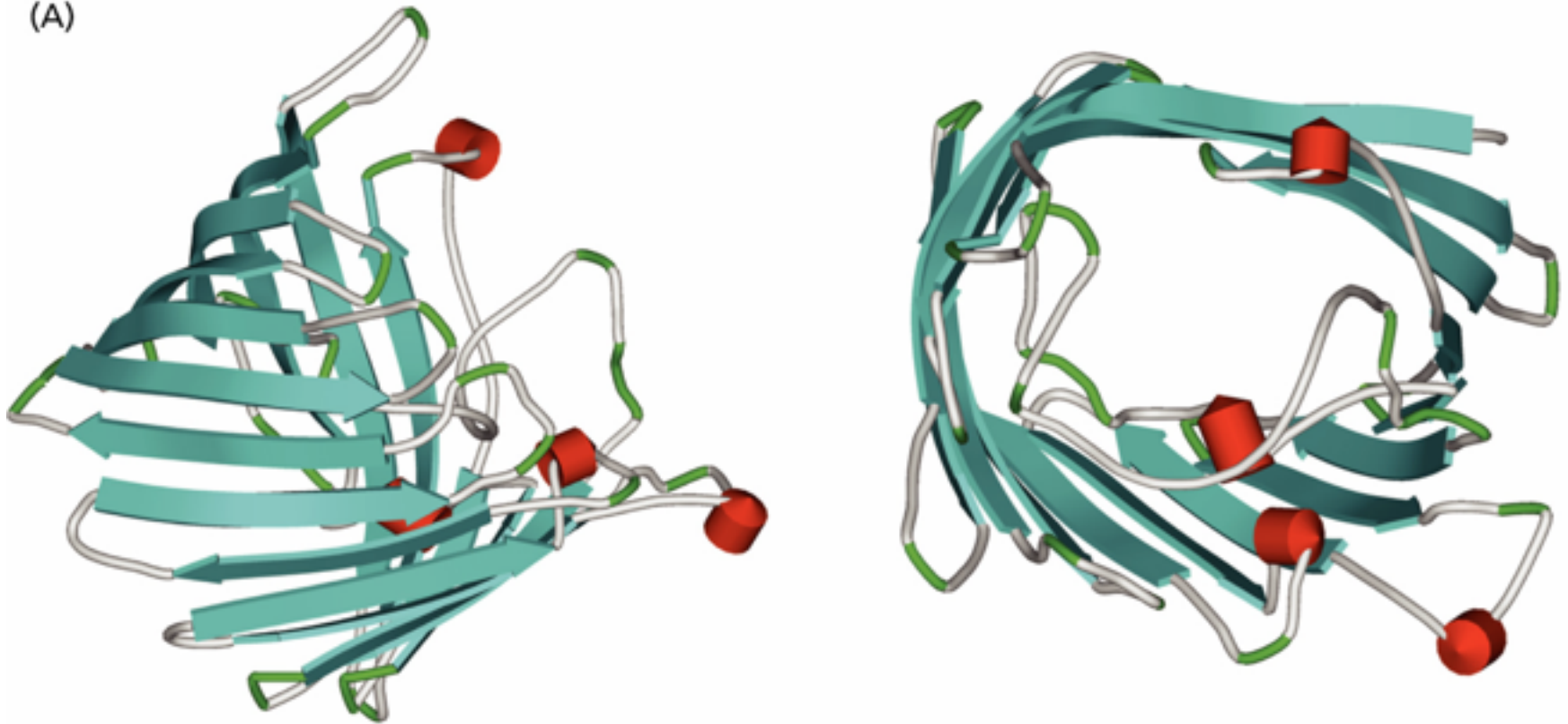


A helix-bundle membrane protein

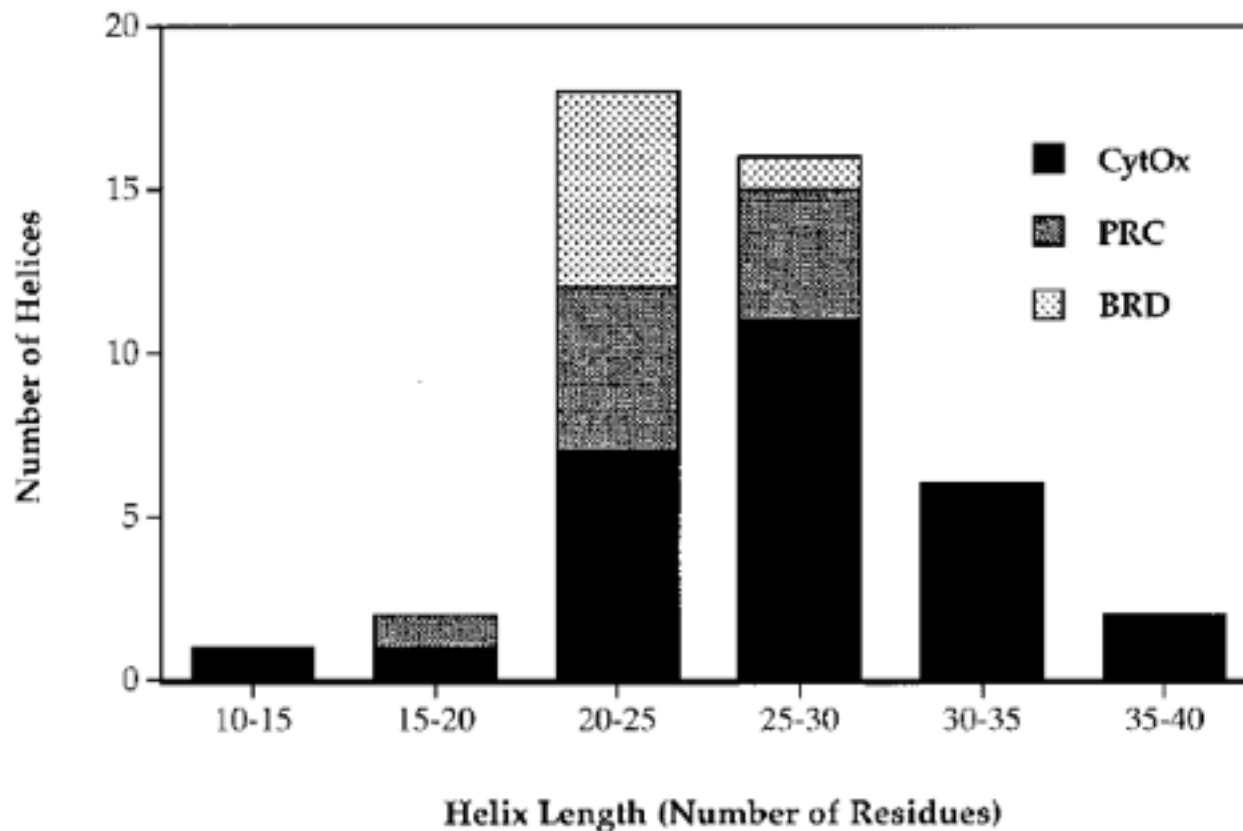


A β -barrel membrane protein

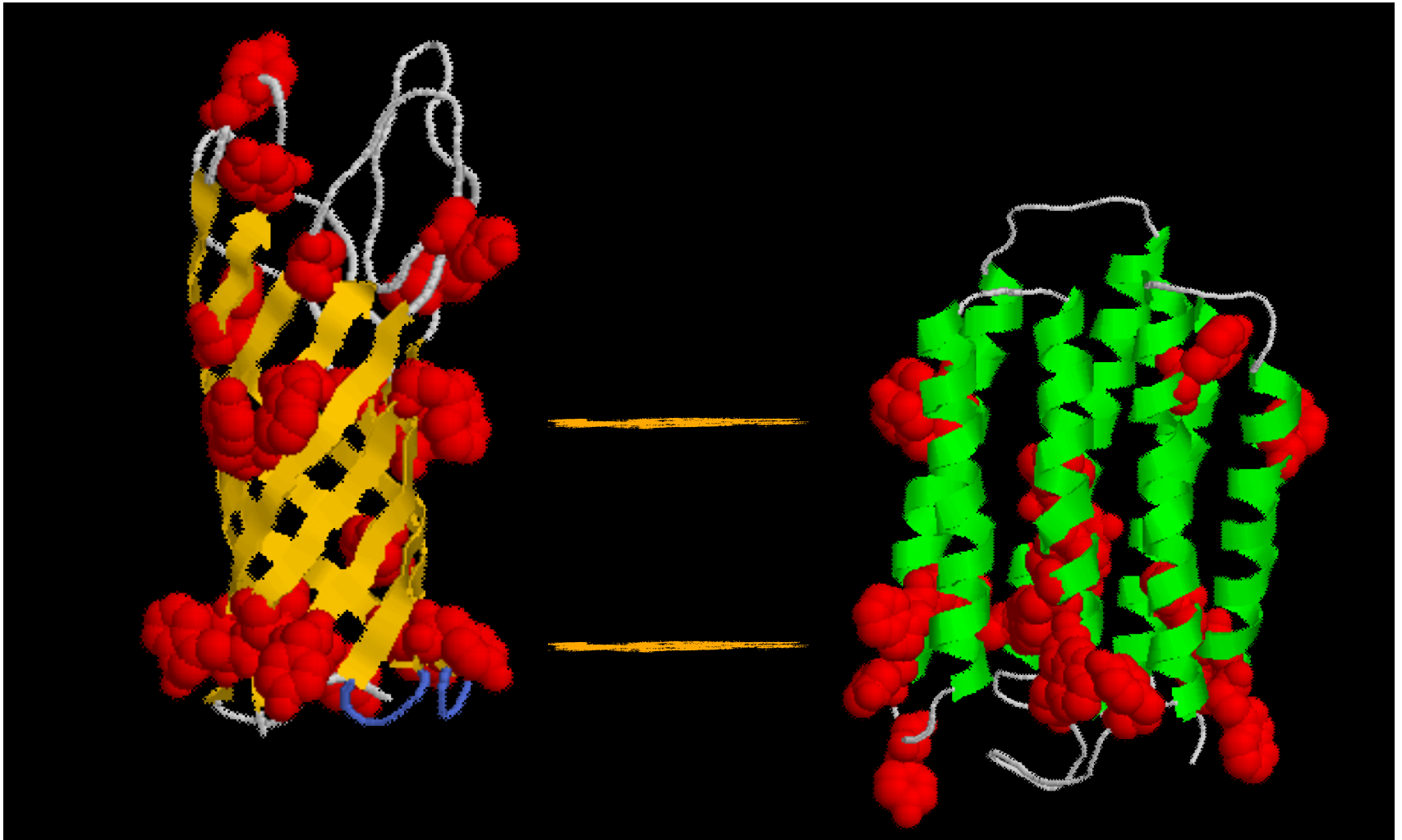
(A)



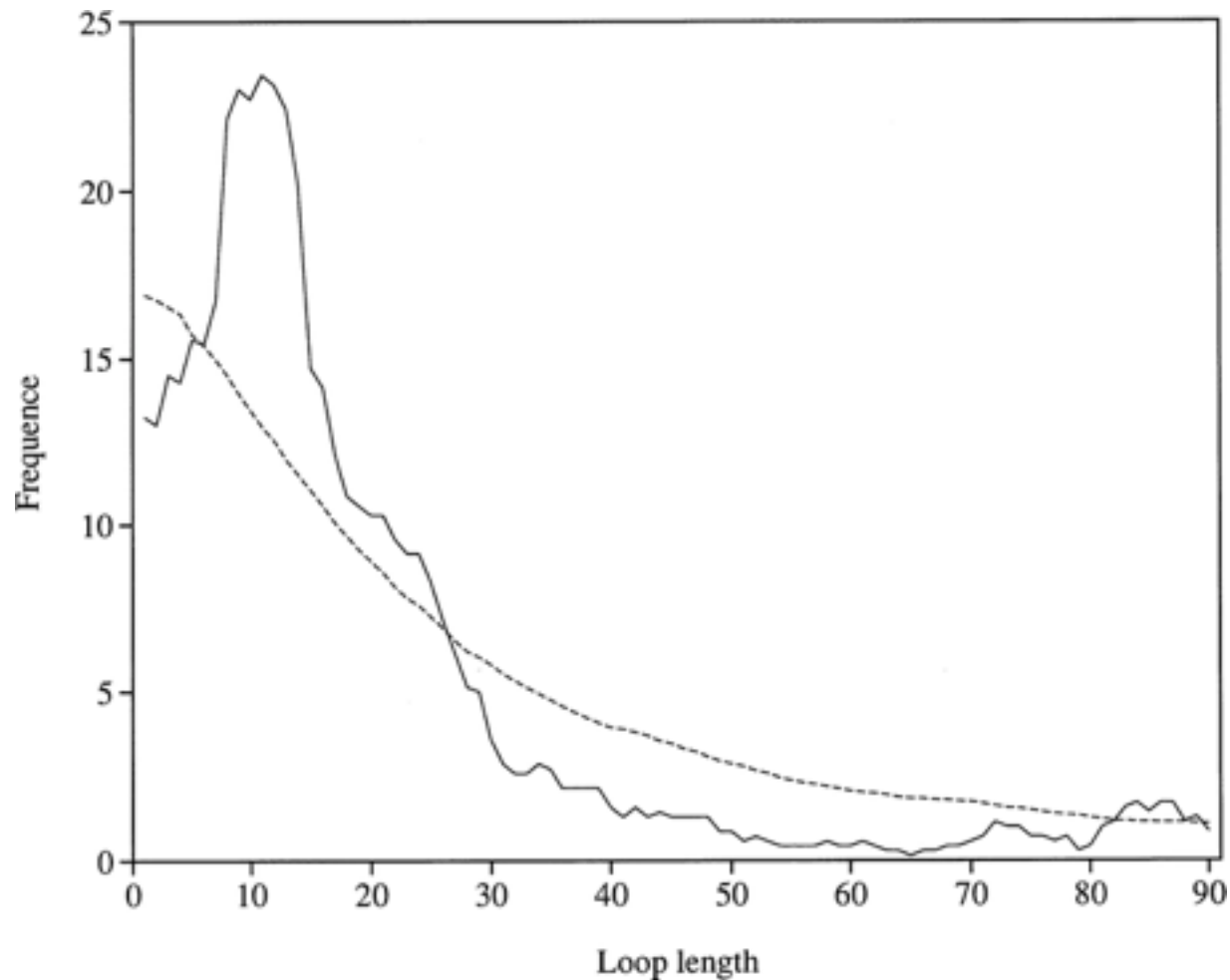
TM helices are typically 20-30 residues long



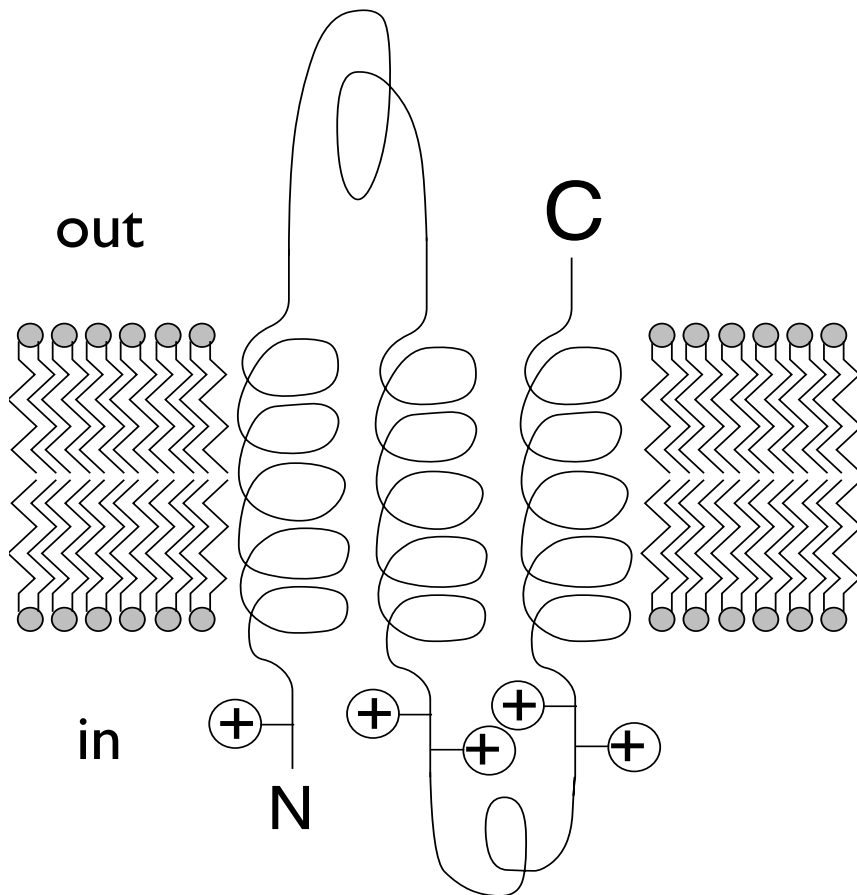
Trp and Tyr are enriched in the lipid headgroup region



Loops connecting the TM helices tend to be short



The positive-inside rule



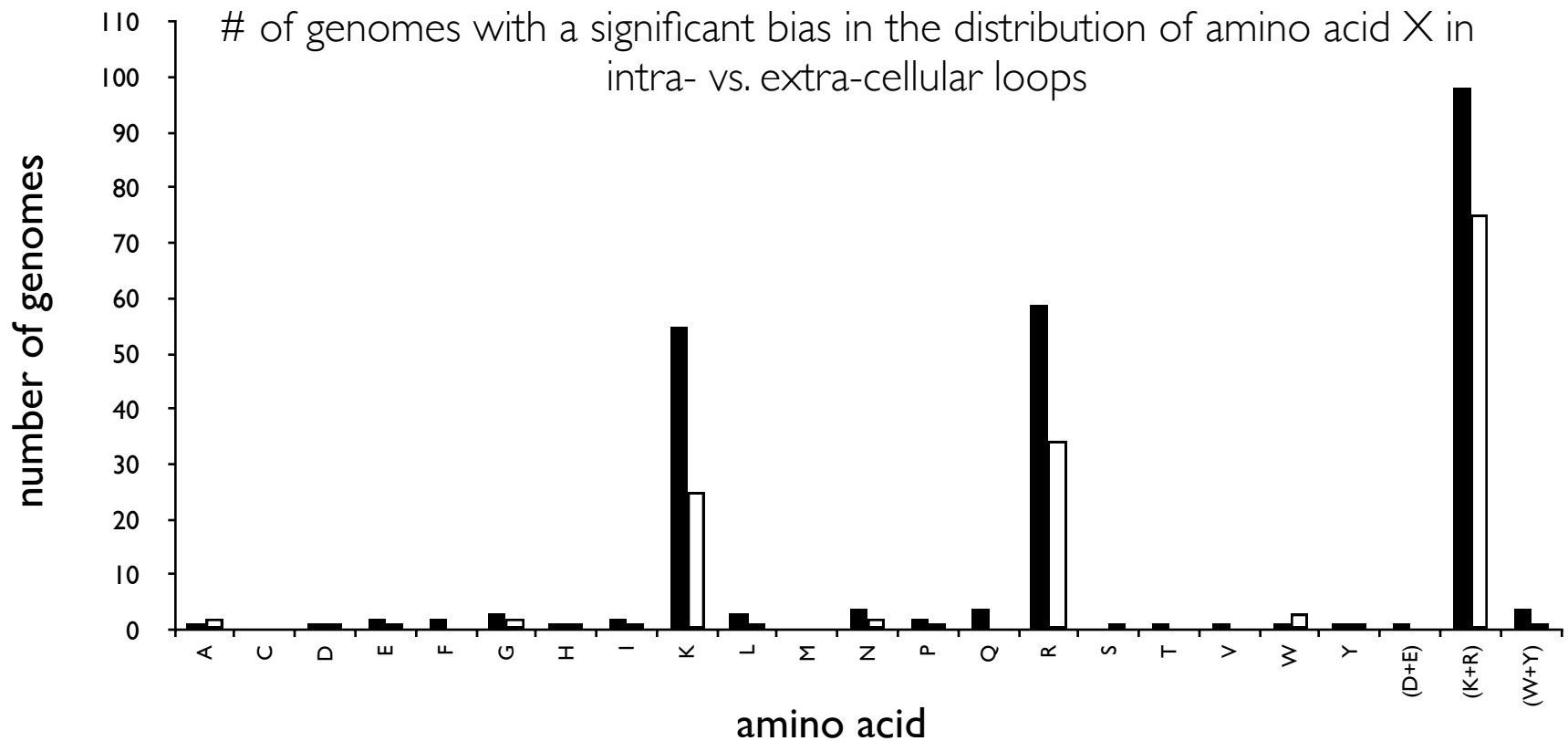
Bacterial inner membrane
in: 16% K+R out: 4% K+R

Eukaryotic plasma membrane
in: 17% K+R out: 7% K+R

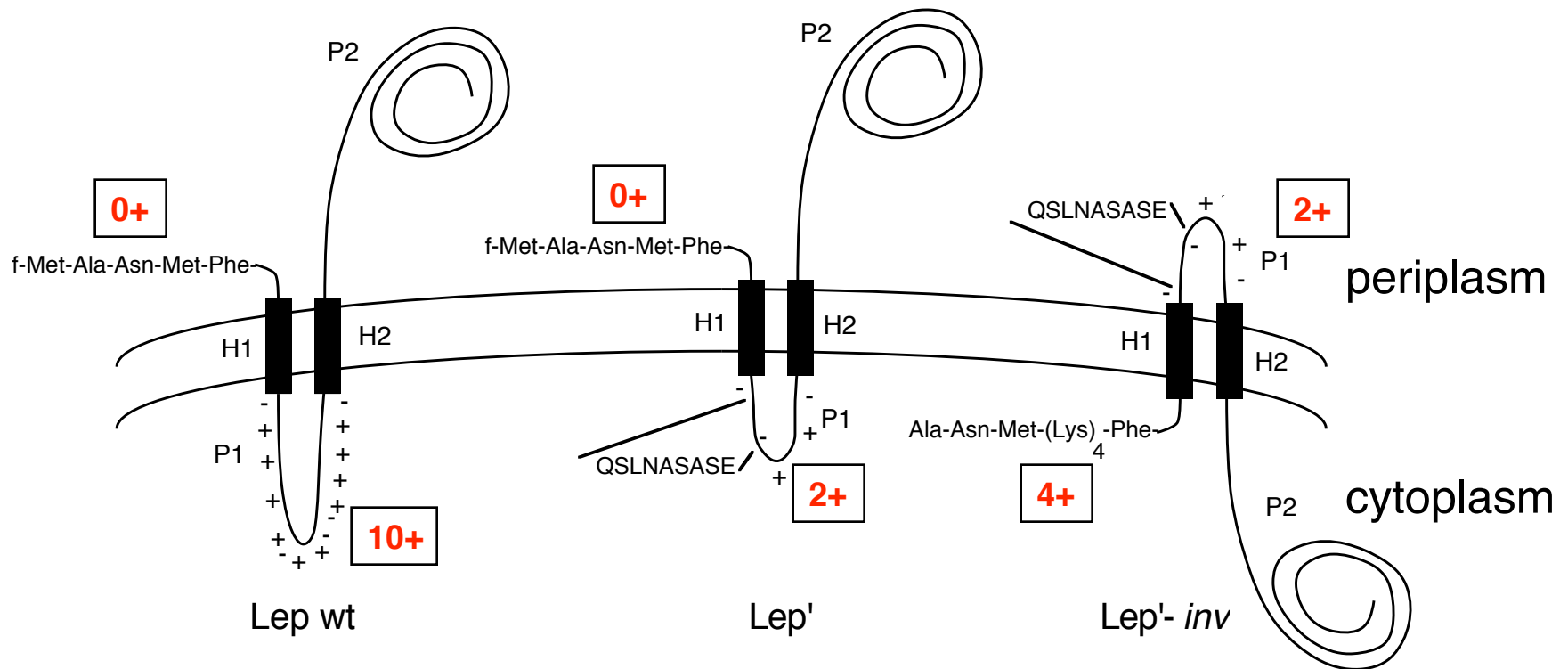
Thylakoid membrane
in: 13% K+R out: 5% K+R

Mitochondrial inner membrane
In: 10% K+R out: 3% K+R

The positive-inside rule applies to all organisms

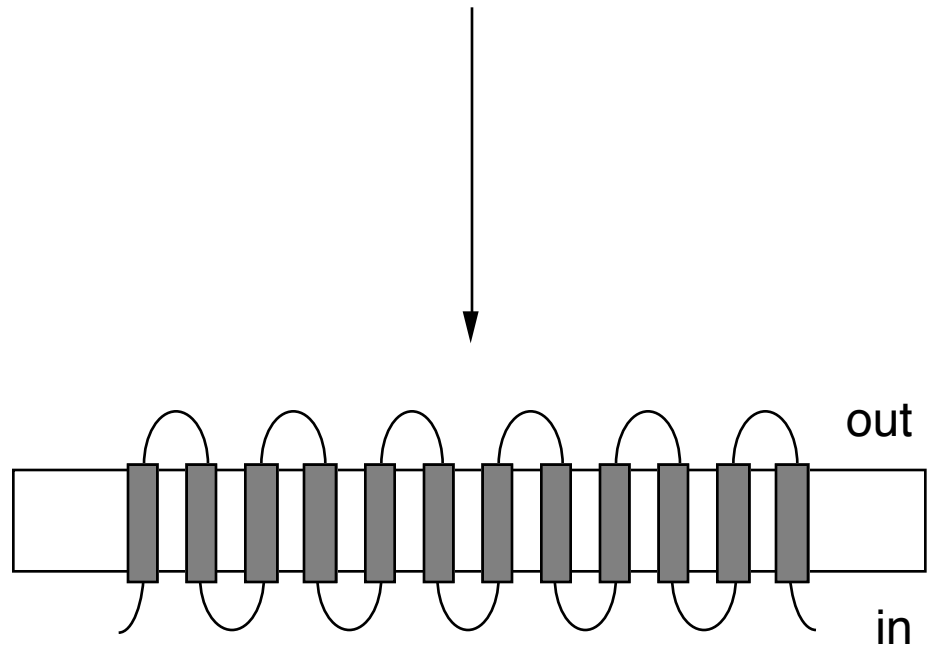


Topology is controlled by positively charged residues

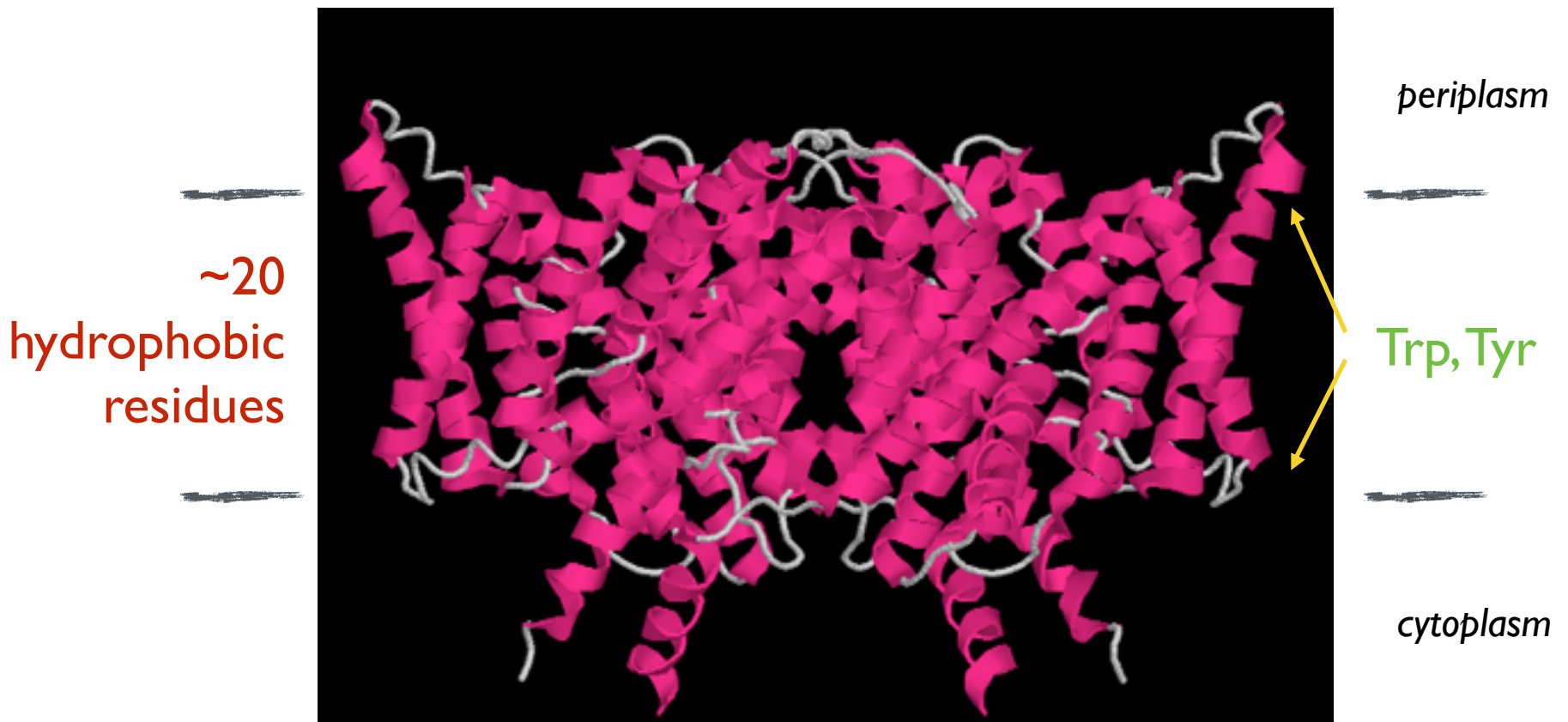


Topology prediction

MDSQRNLLVIALLFVSFMIWQAW... ..

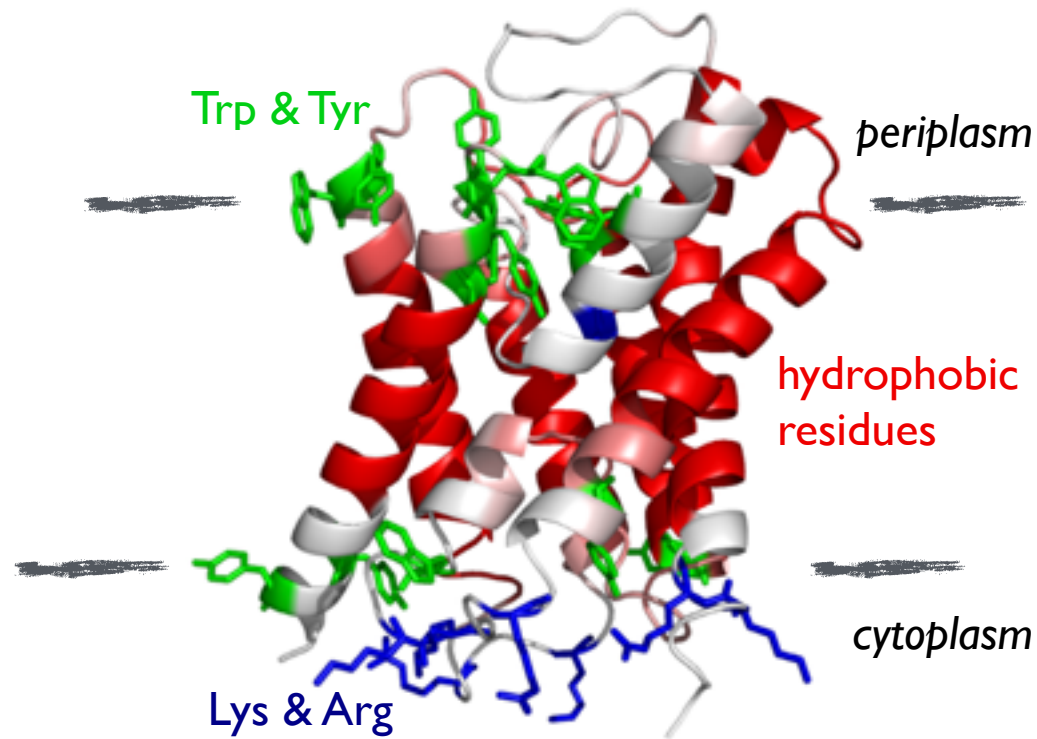


The three most important characteristics



The positive-inside rule

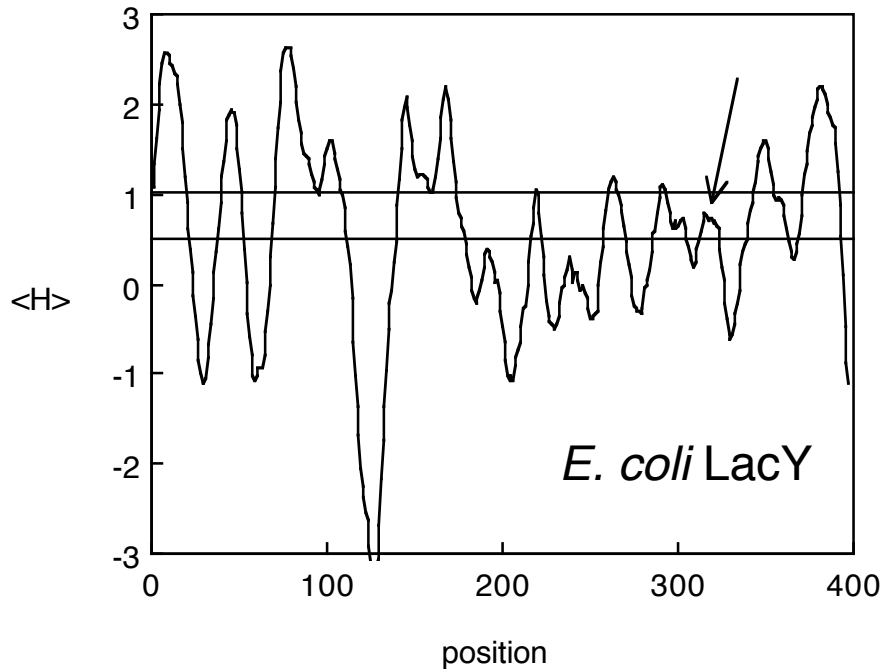
The three most important characteristics



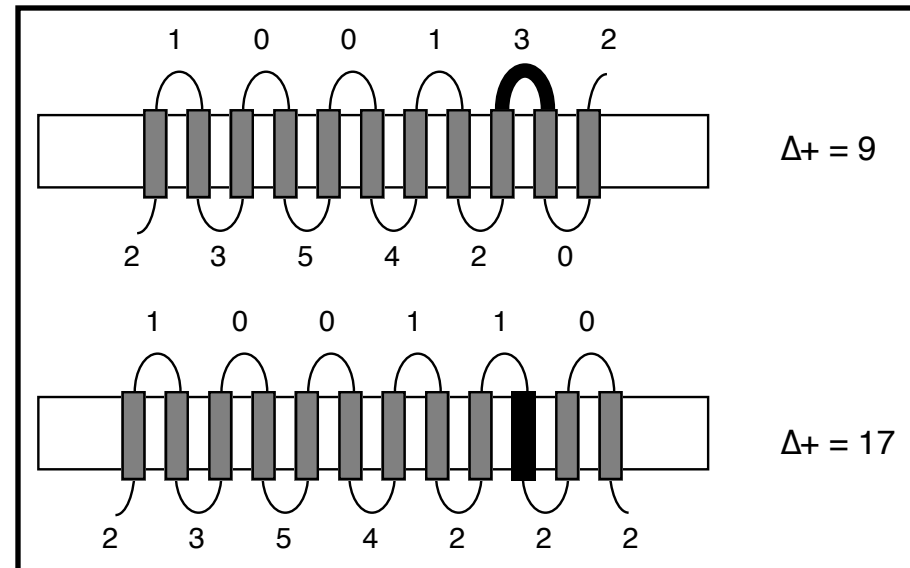
Popular topology predictors

TMHMM (HMM)
HMMTOP (HMM)
Prodiv-TMHMM (MSA, HMM)
Phobius (HMM)
MEMSAT (MSA, dynamic programming)
TOPCONS (consensus method)
....
SCAMPI (h-plot, PI-rule)
PHD (MSA, NN, PI-rule)
TopPred (h-plot, PI-rule)
....
Kyte & Doolittle (h-plot)
SOAP (h-plot)

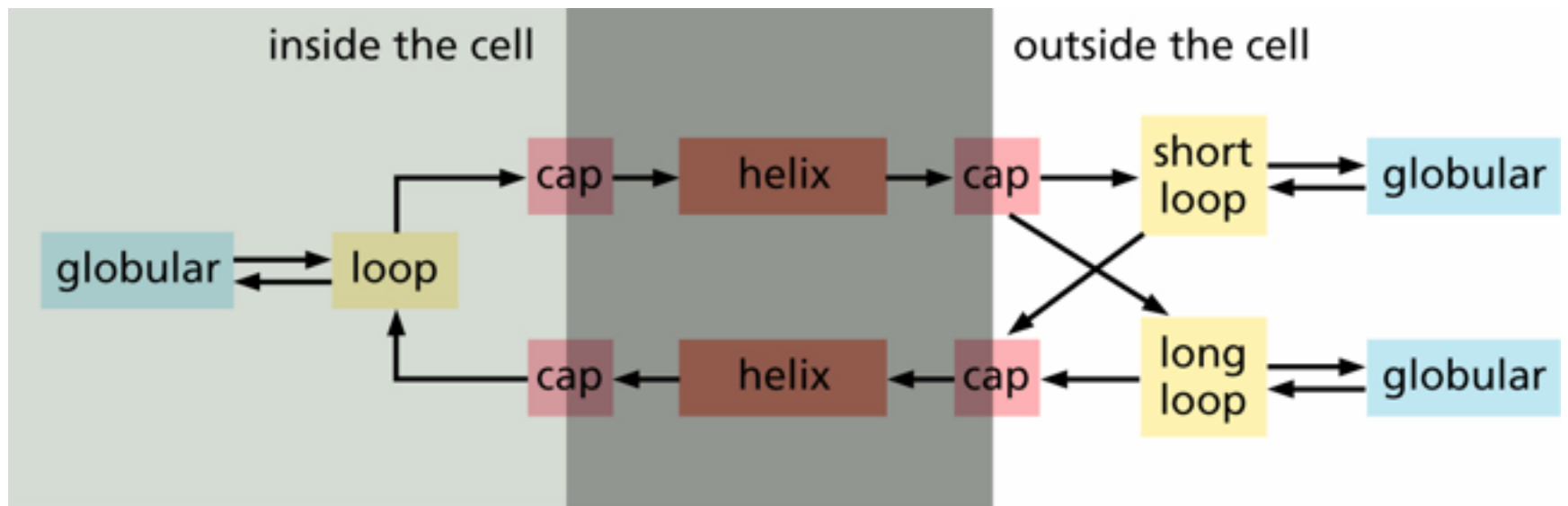
TopPred



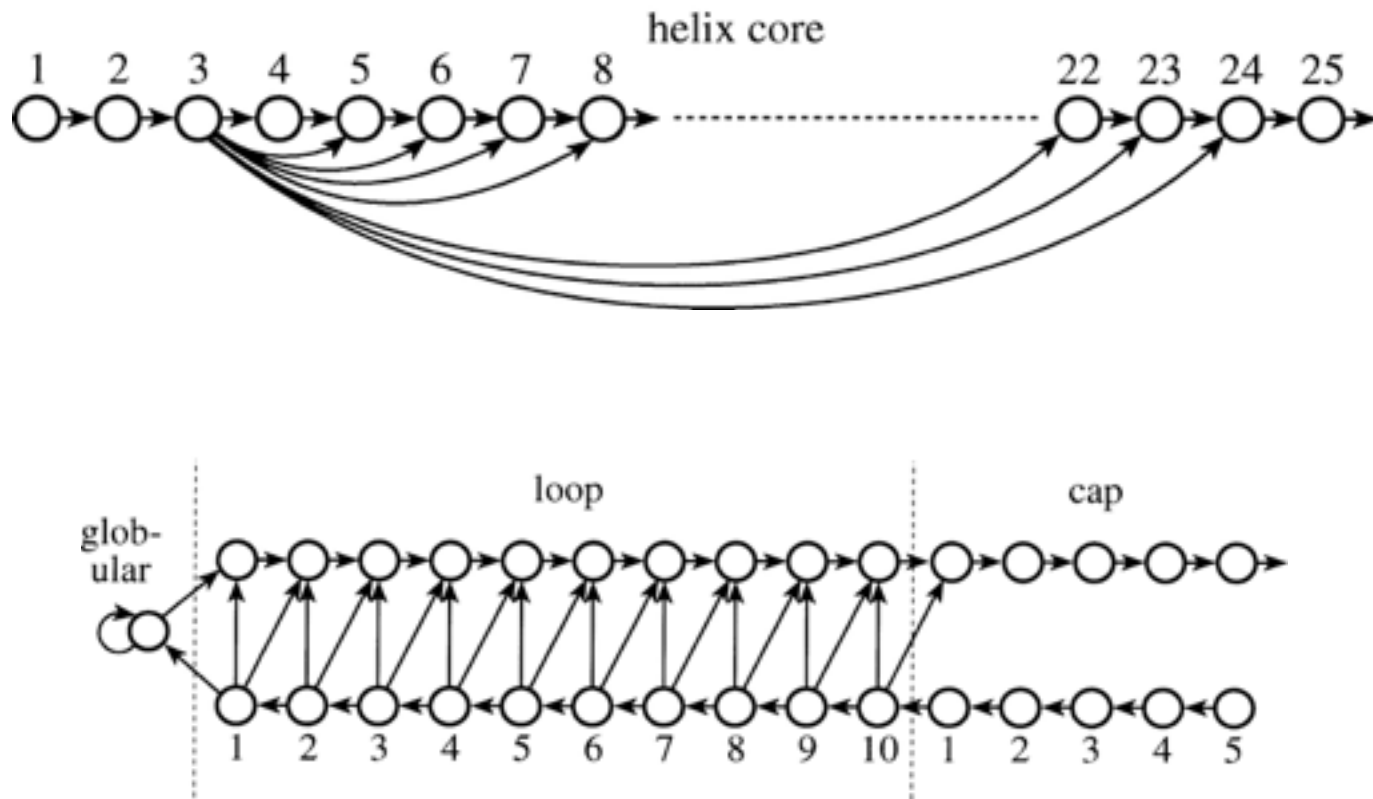
- construct all possible topologies
- rank based on $\Delta+$



TMHMM



Helix and loop models in TMHMM



TOPCONS

TOPCONS: Consensus prediction of membrane protein topology

http://topcons.cbr.su.se/

DN.se - Nyheter - Nyheter - Cvh bookmarks - Google - Entrez Browser - Apple .Mac Login - Apple - SU mail - PubMed: membra... - MP book

TOPCONS Sunday, September 13 2009

TOPCONS

Main Menu

- New query
- SCAMPI
- OCTOPUS
- ΔG -scale
- ZPRED
- PRO/PRODIV
- Help

Consensus prediction of membrane protein topology

For large benchmark sets and full proteome scans, use the [SCAMPI server](#) instead. This server is free for academic use.

Enter one amino acid sequence in [FASTA](#) format

Restraint options ▶

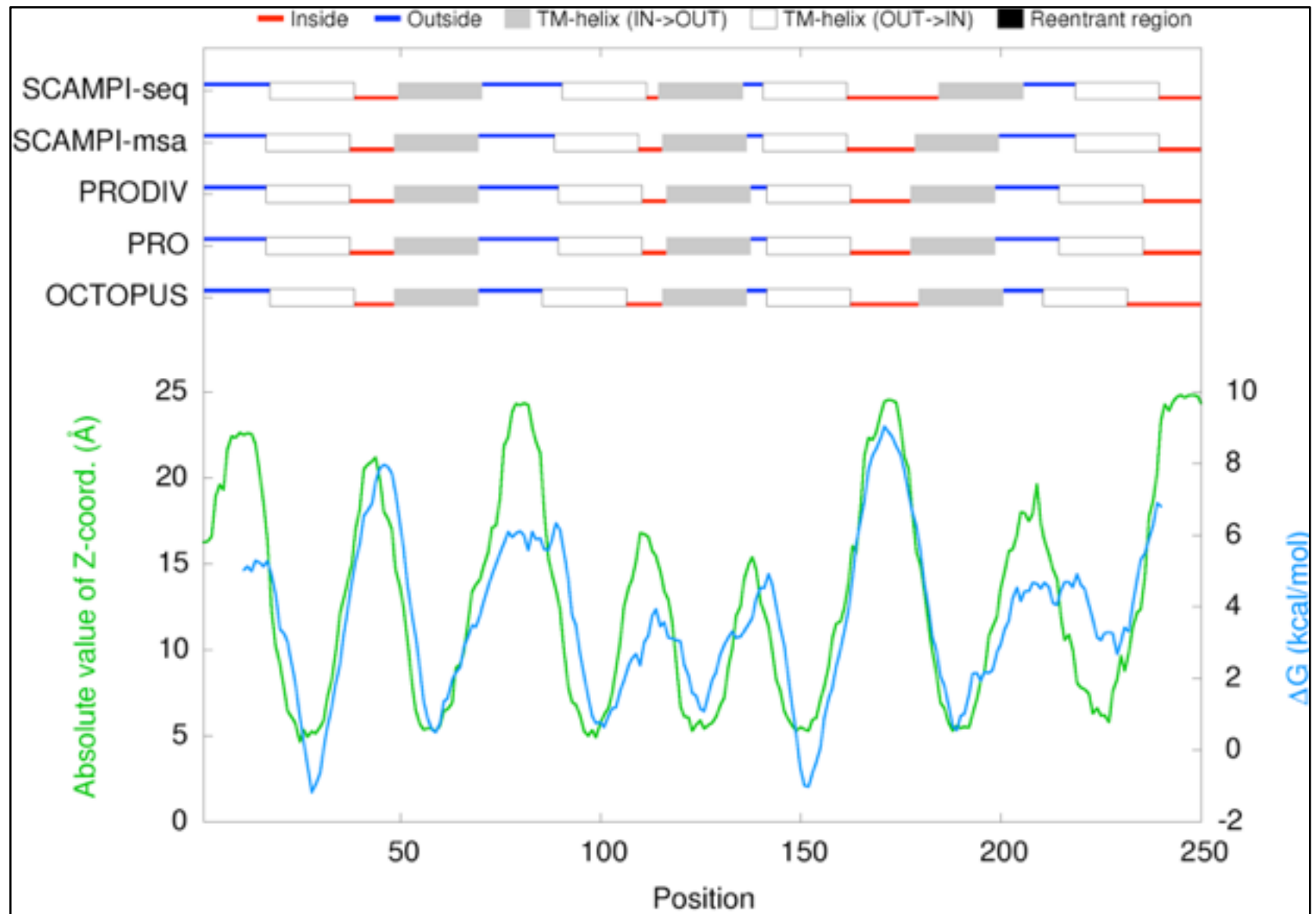
References

TOPCONS:
TOPCONS: Consensus prediction of membrane protein topology. A Bernsel, H Viklund, A Hennerdal and A Elofsson (2009) *Nucleic Acids Research* in press

SCAMPI:
Prediction of membrane-protein topology from first principles. Andreas Bernsel, Håkan Viklund,

Klar

TOPCONS

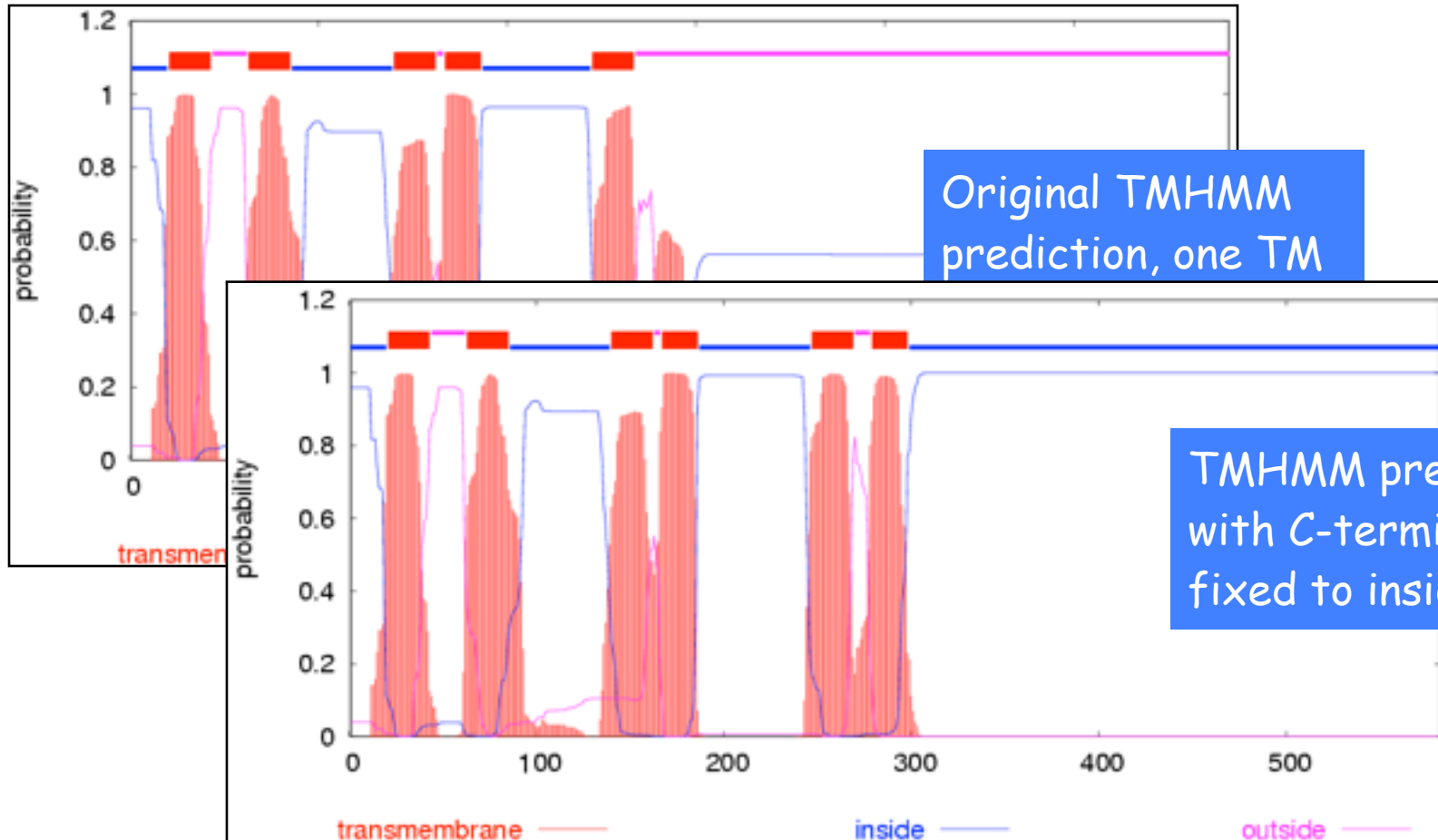


How good are topology predictors?

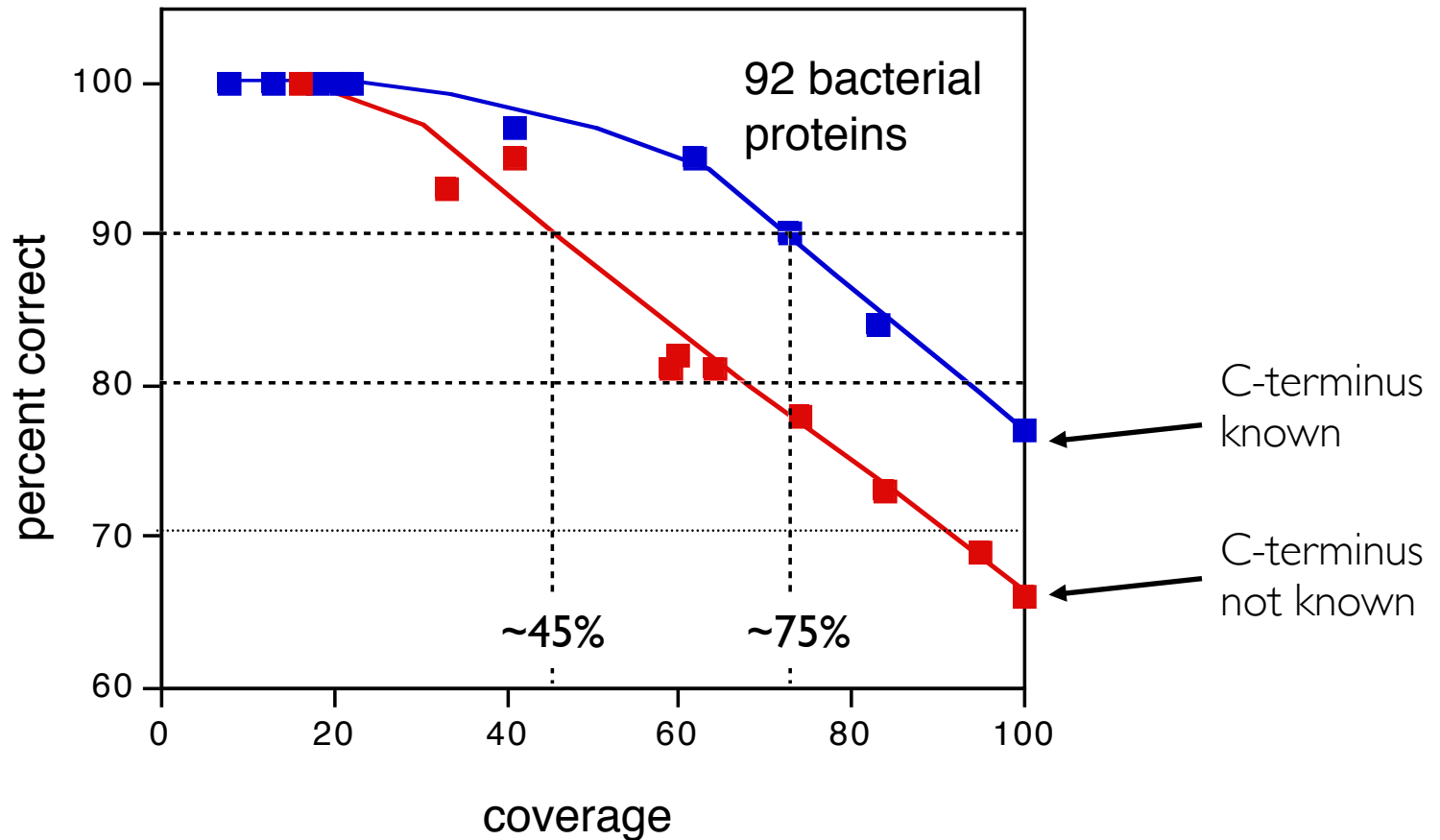
Discrimination membrane/soluble: sensitivity 97%; specificity 95%

Topology: single sequence 70-75%; multi-sequence 80-85%

Experimental constraints help



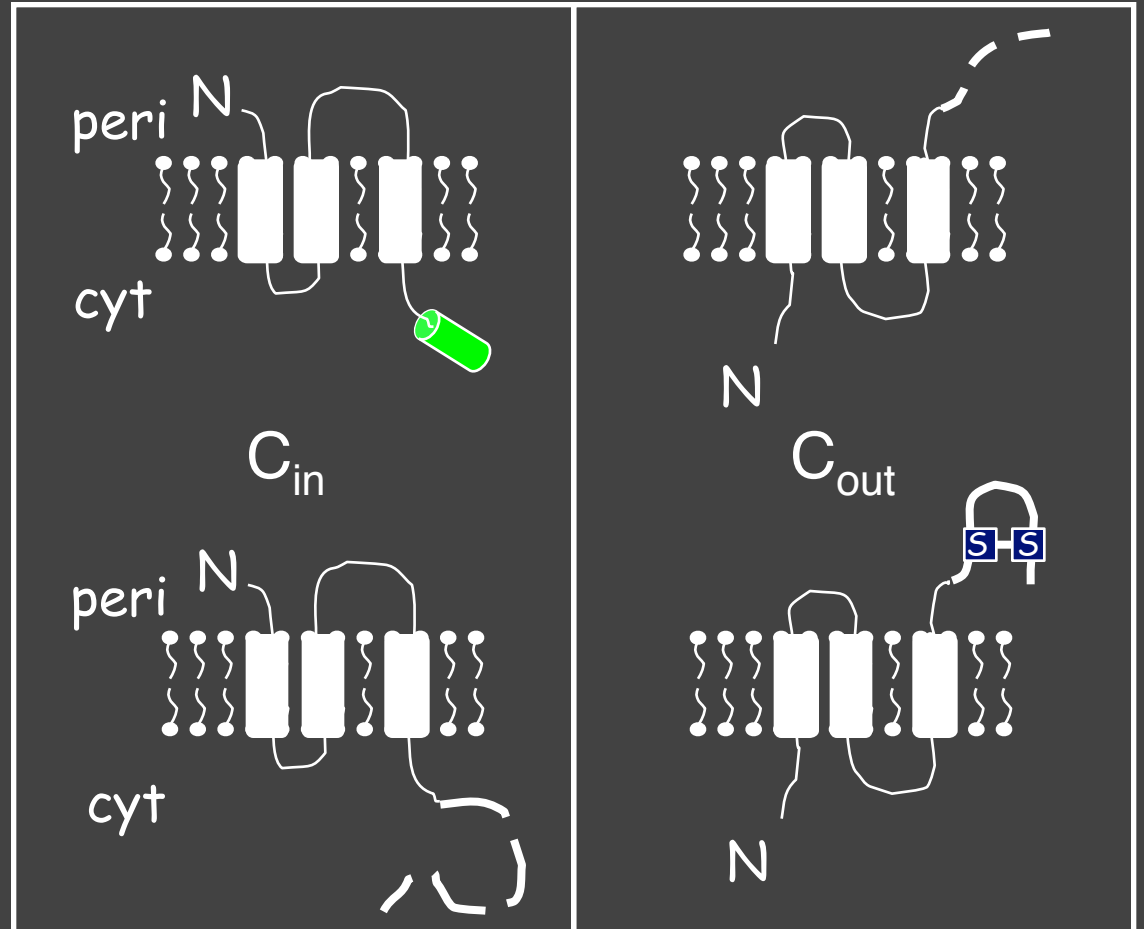
Experimental constraints help



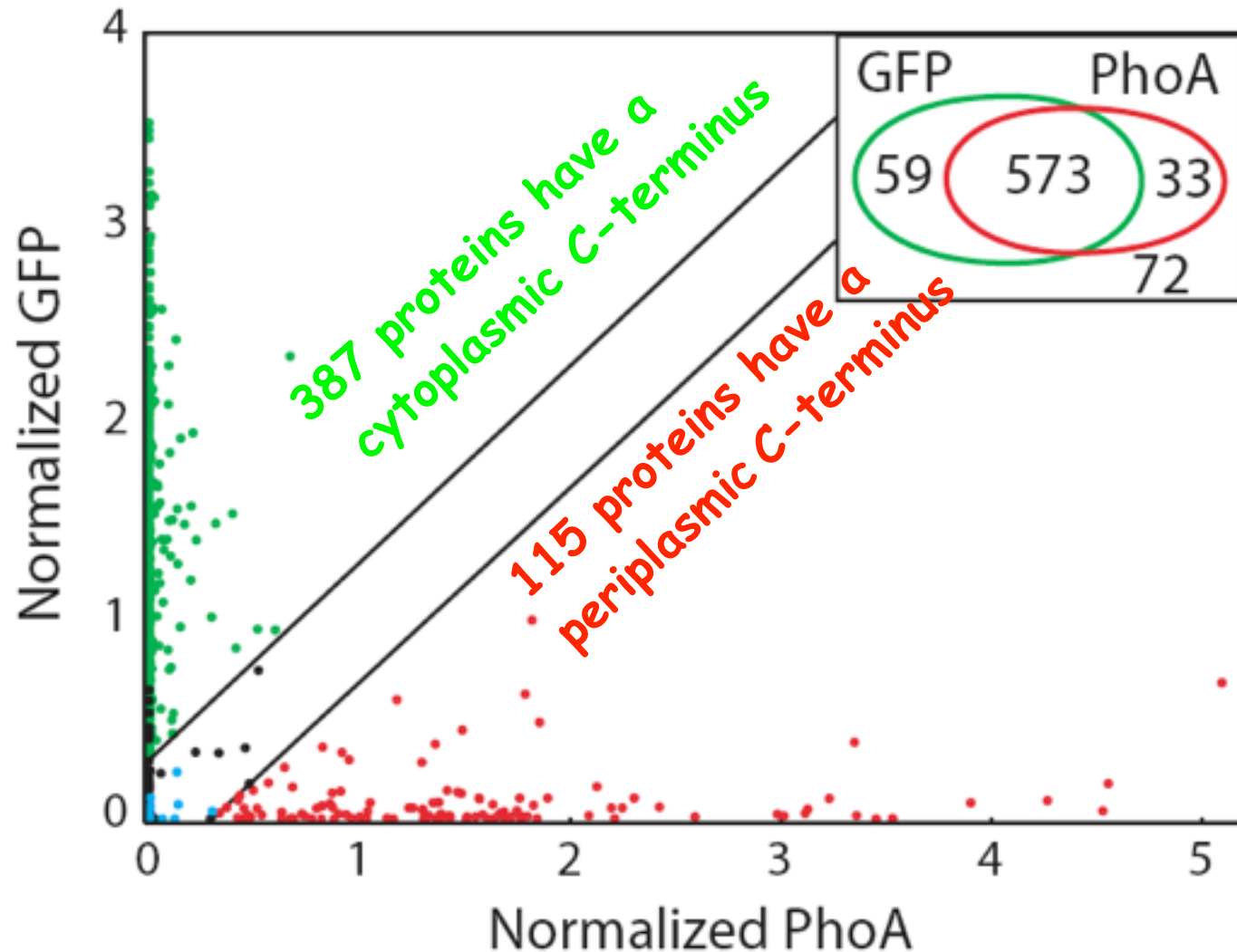
Experimental constraints help

GFP is only active
in the cytoplasm

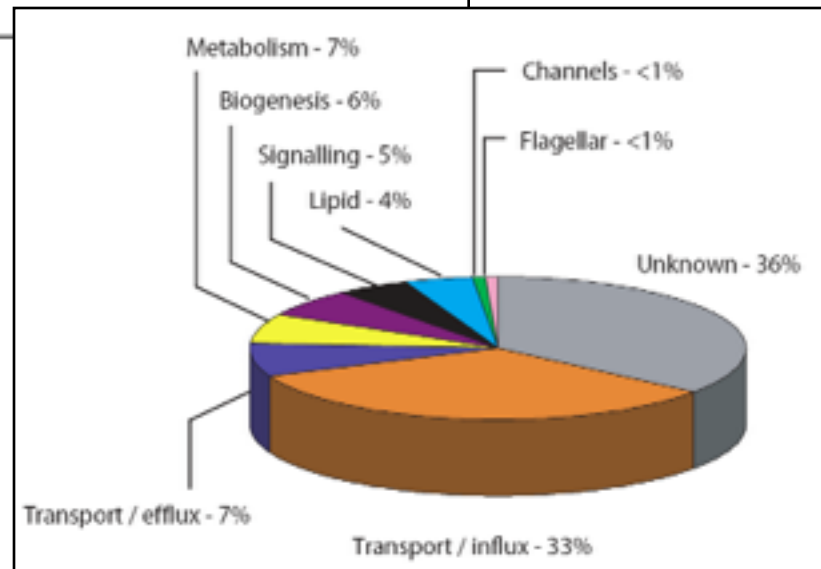
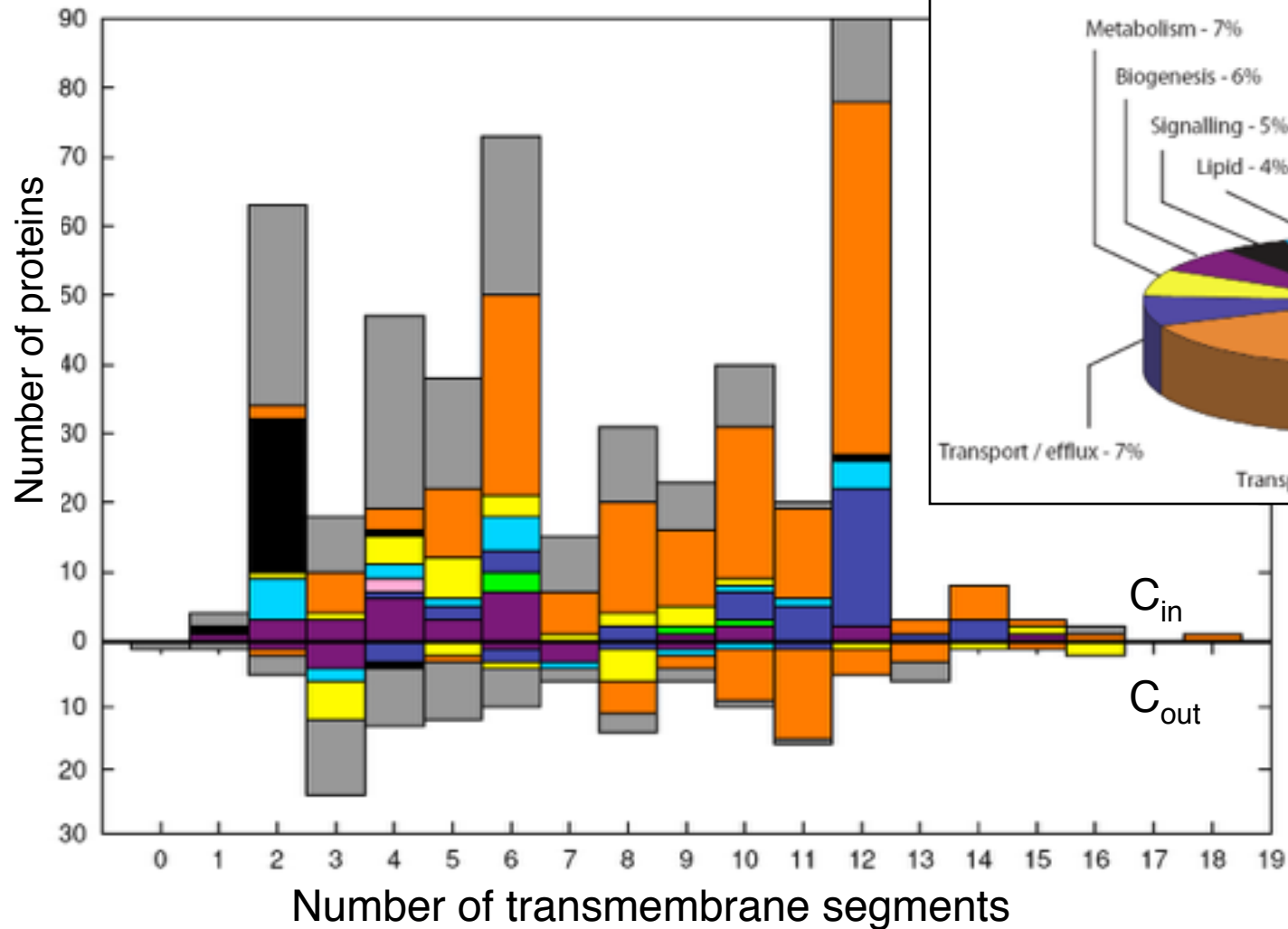
PhoA is only active
in the periplasm



Experimental constraints help



Experimental constraints help

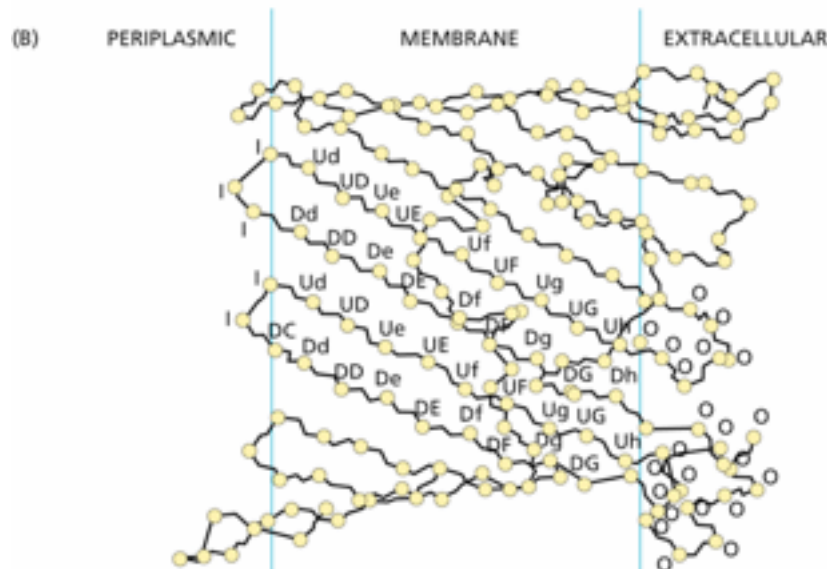
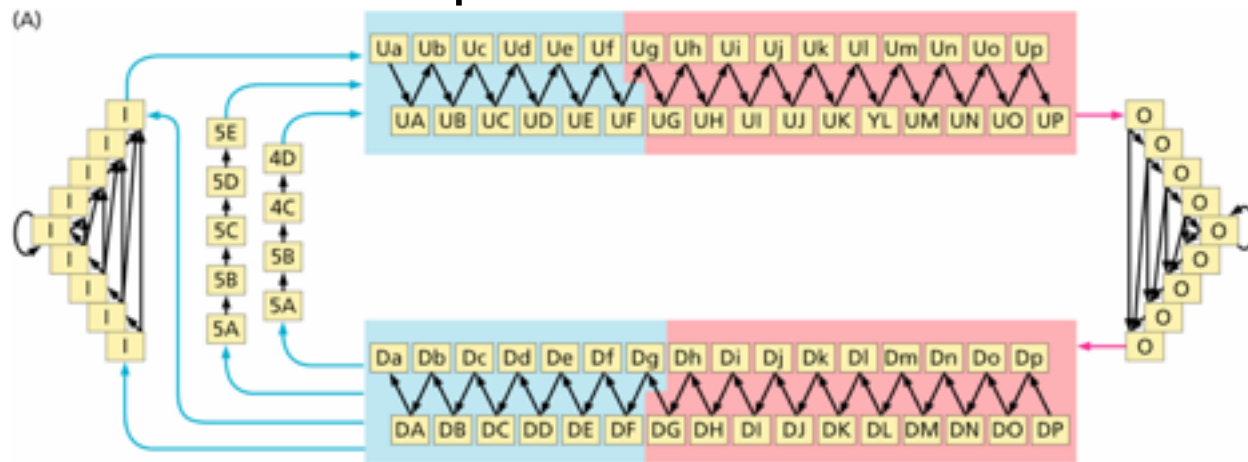


'Exporting' experimental constraints using alignments



225/38 bacterial/eukaryotic genomes
158 k/139 k predicted membrane proteins
51.000/15.000 assignments

A HMM for β -barrel membrane proteins



Don't forget...

Two architectures: helix bundle and β -barrel

Hydrophobic transmembrane helices

Alternating Hyf-X β -strands

The positive-inside rule

TopPred

TMHMM

TOPCONS

Experimental constraints help