

# Prediction of membrane protein topology

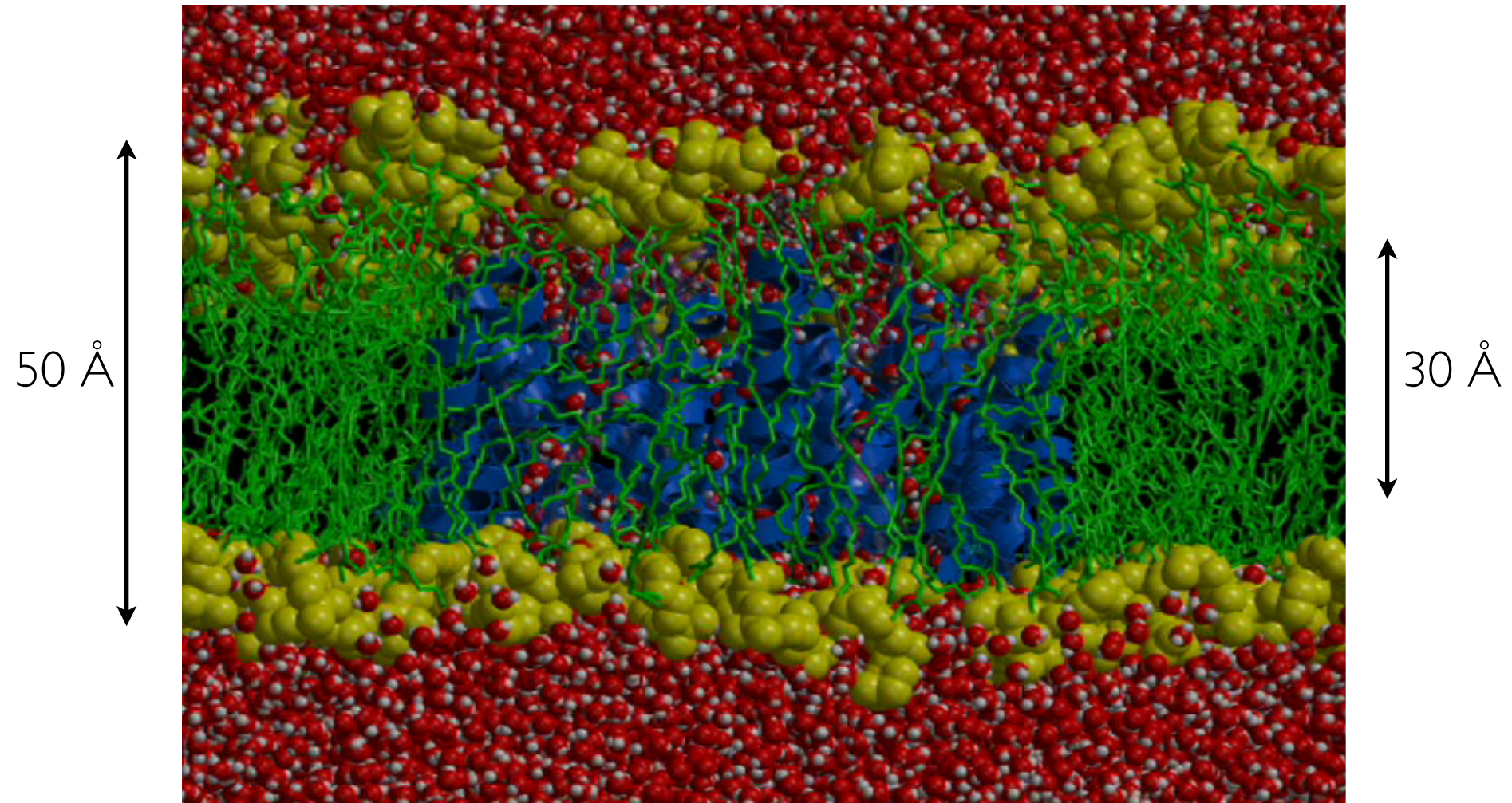
Gunnar von Heijne

Department of Biochemistry and Biophysics  
Stockholm University & SciLifeLab

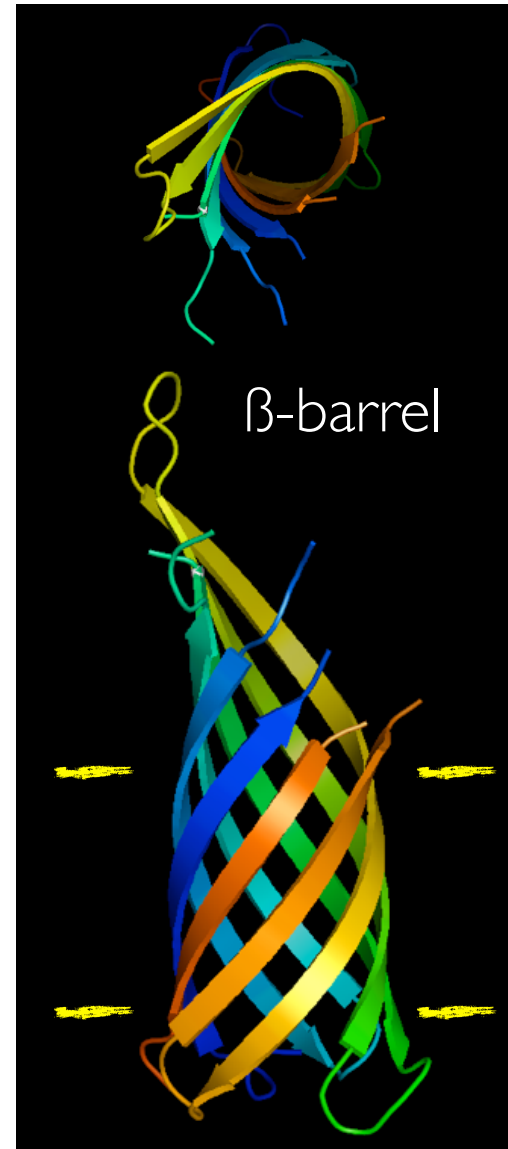
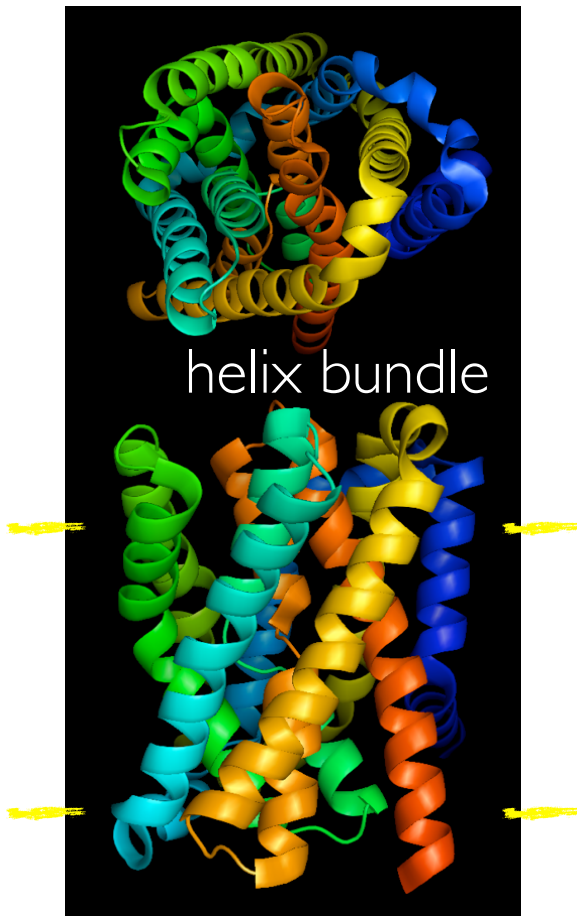


SciLifeLab

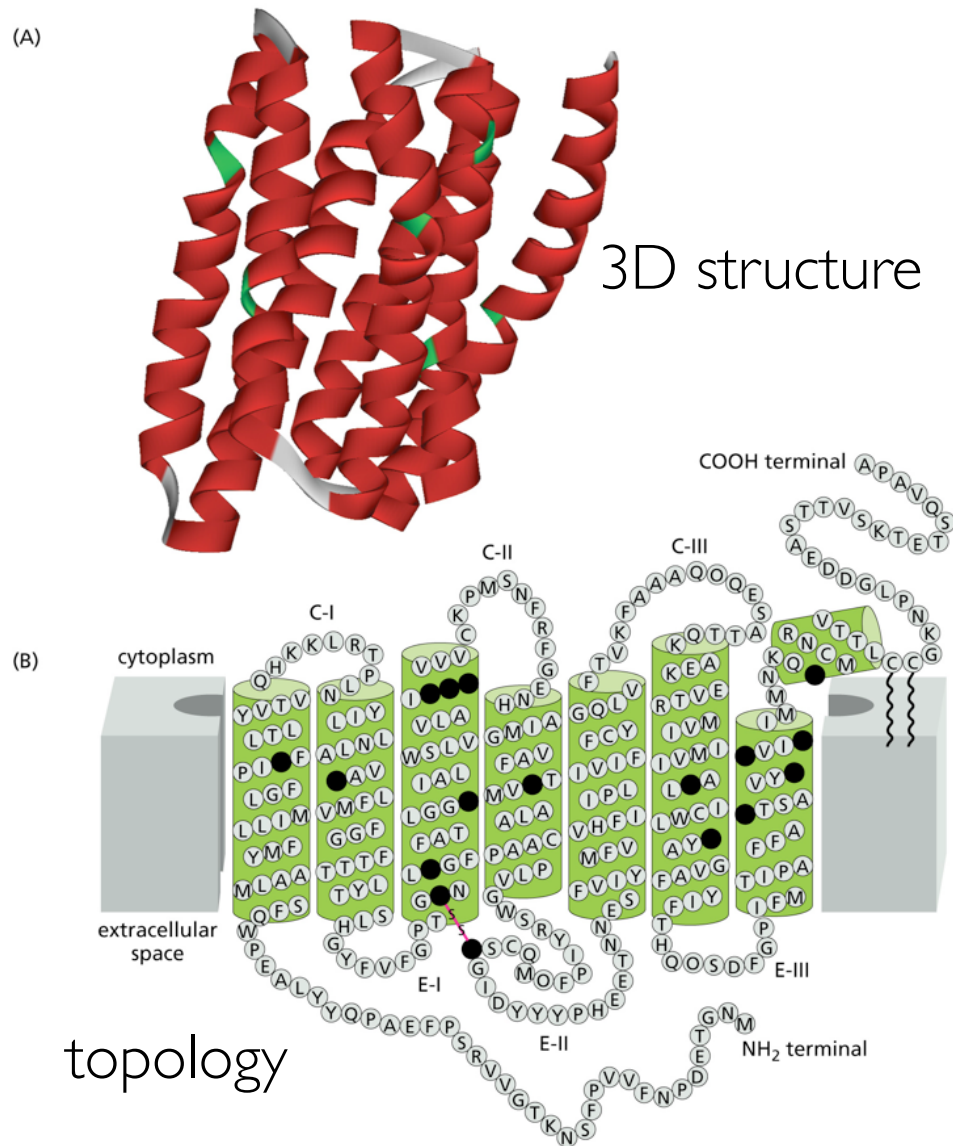
# A simulated membrane



# Only two basic architectures

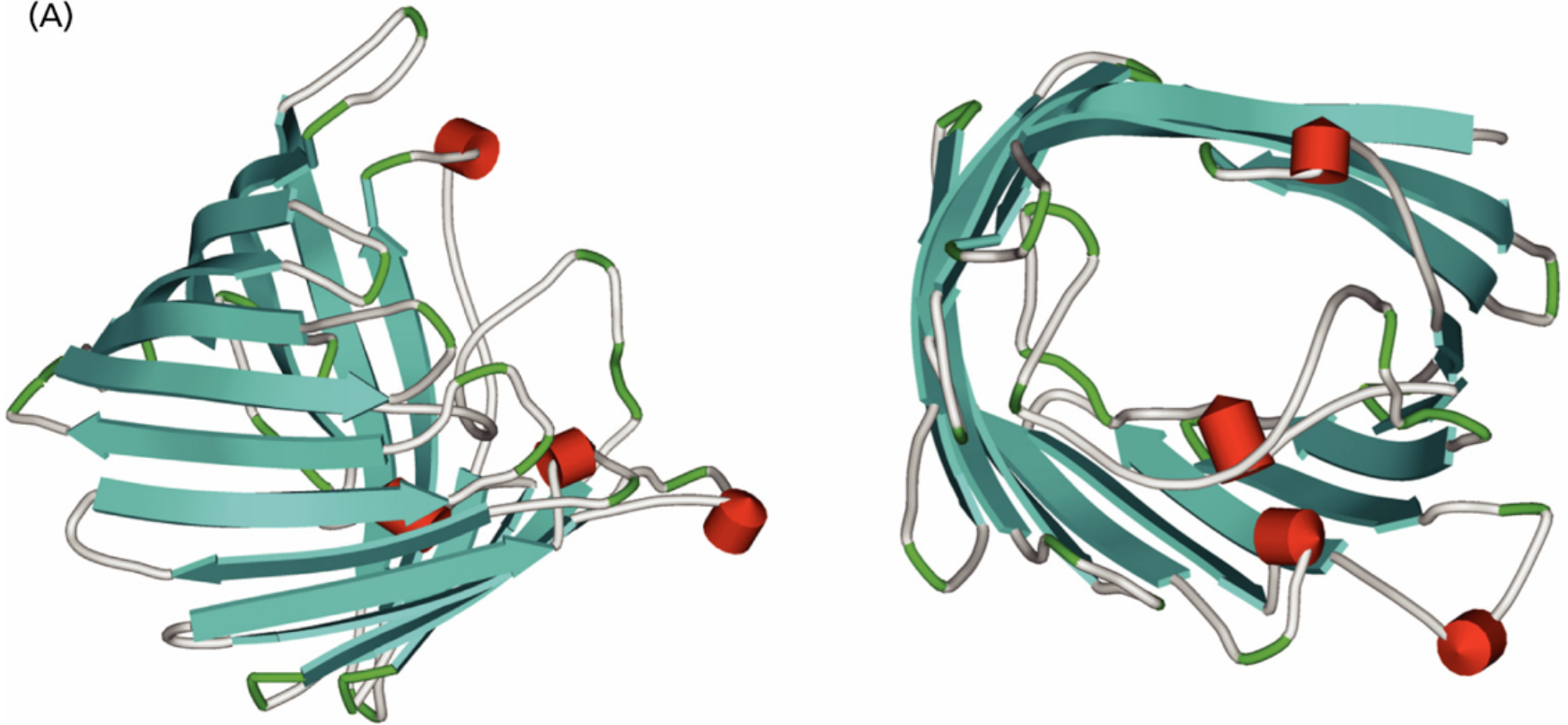


# A helix-bundle membrane protein

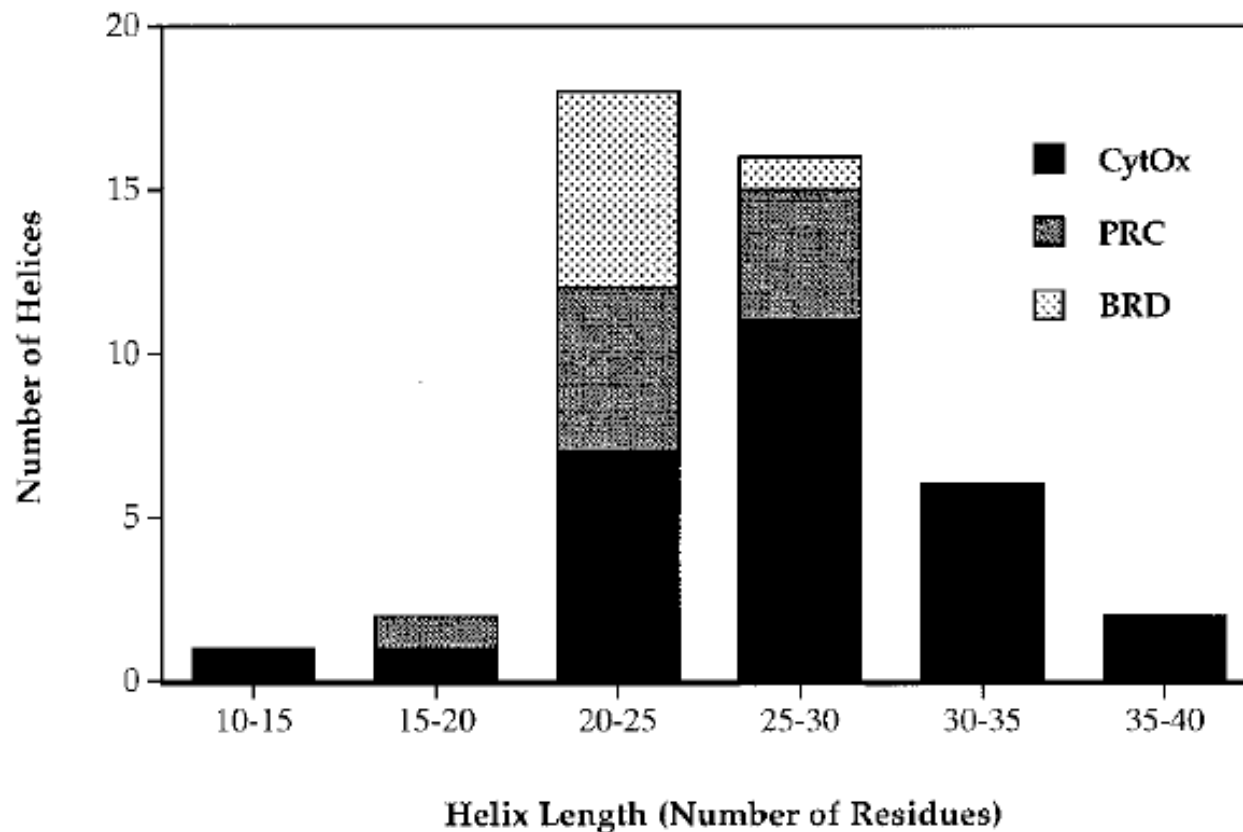


# A $\beta$ -barrel membrane protein

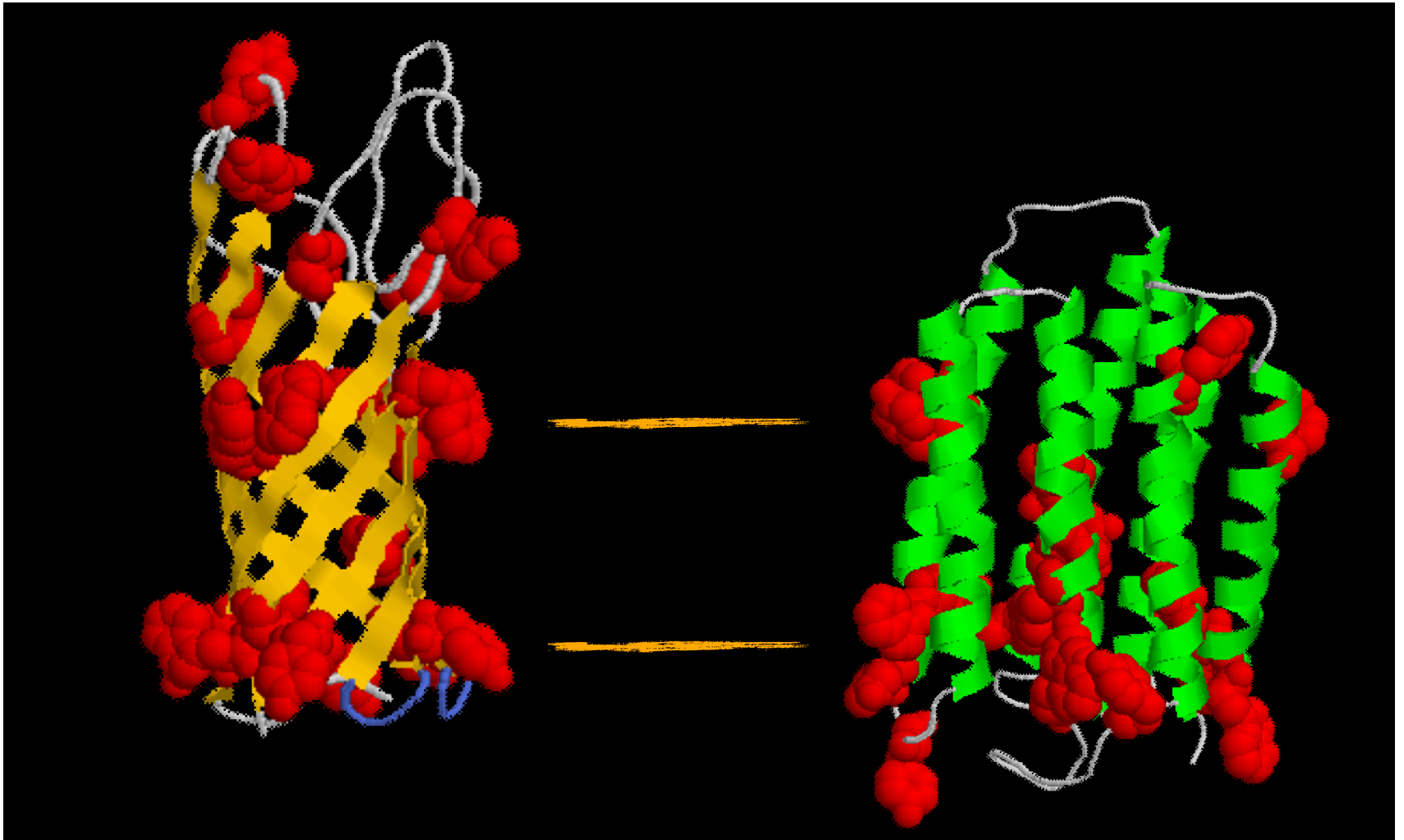
(A)



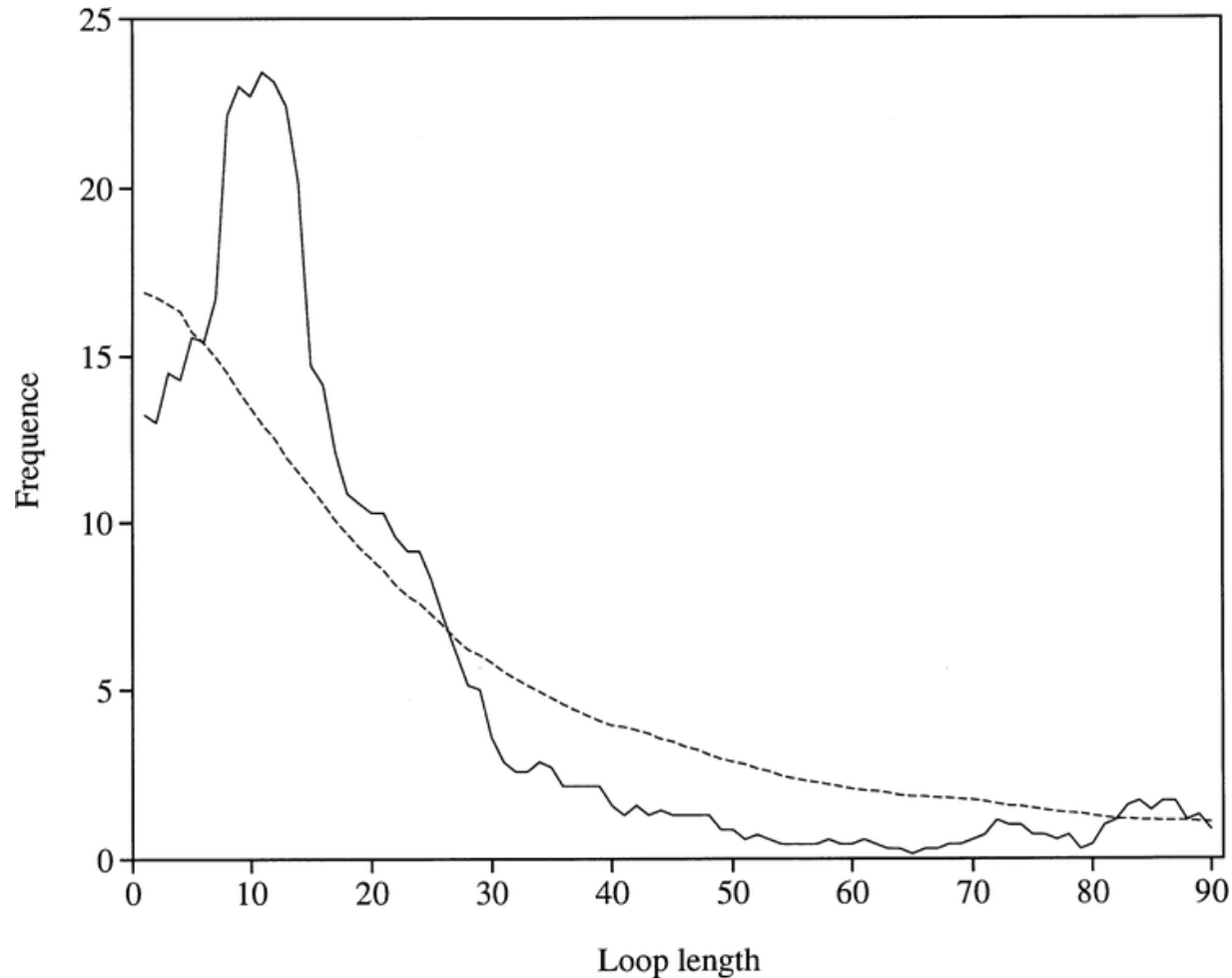
TM helices are typically 20-30 residues long



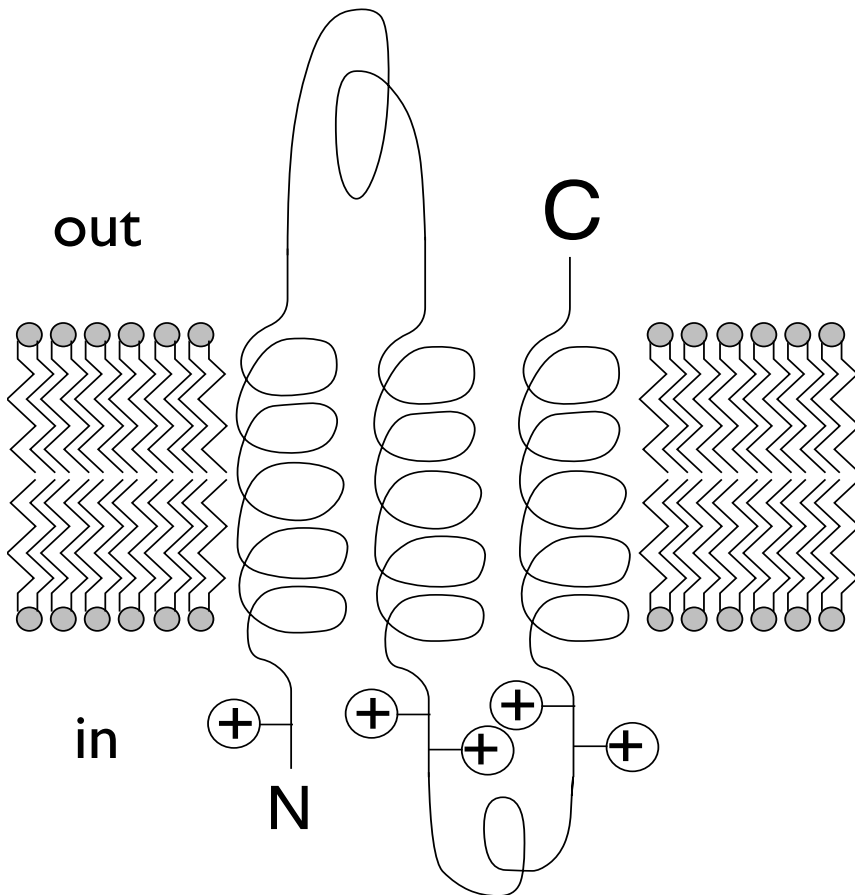
Trp and Tyr are enriched in the lipid headgroup region



# Loops connecting the TM helices tend to be short



# The positive-inside rule



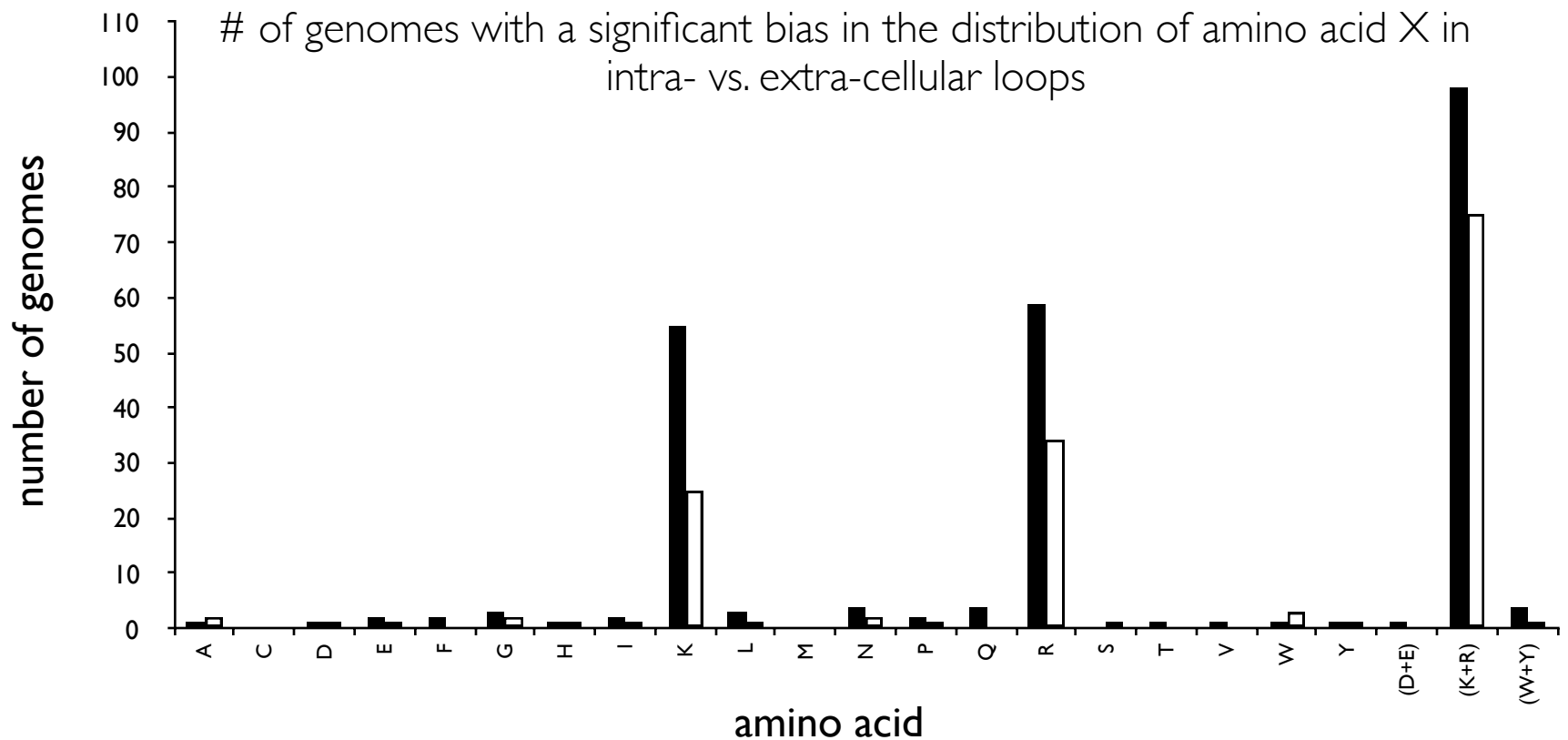
Bacterial inner membrane  
in: 16% K+R out: 4% K+R

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

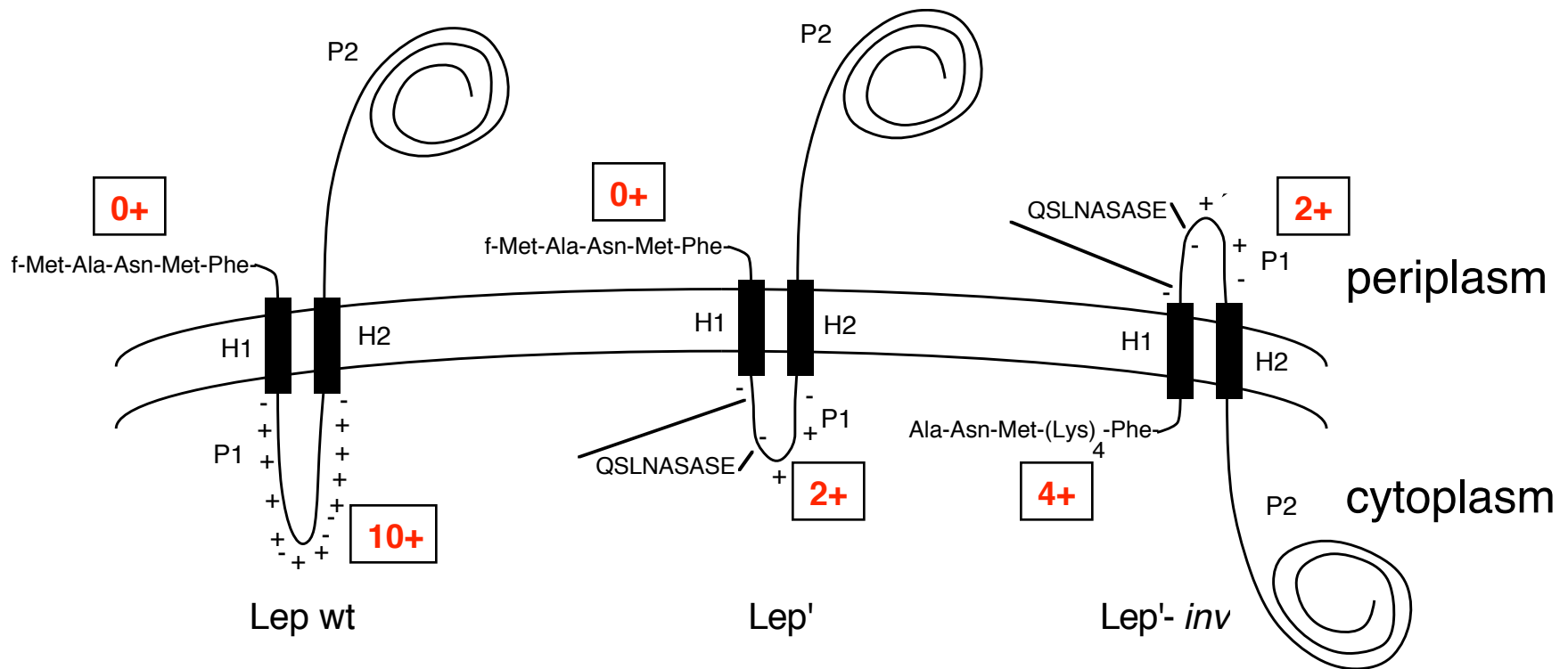
Thylakoid membrane  
in: 13% K+R out: 5% K+R

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

# The positive-inside rule applies to all organisms

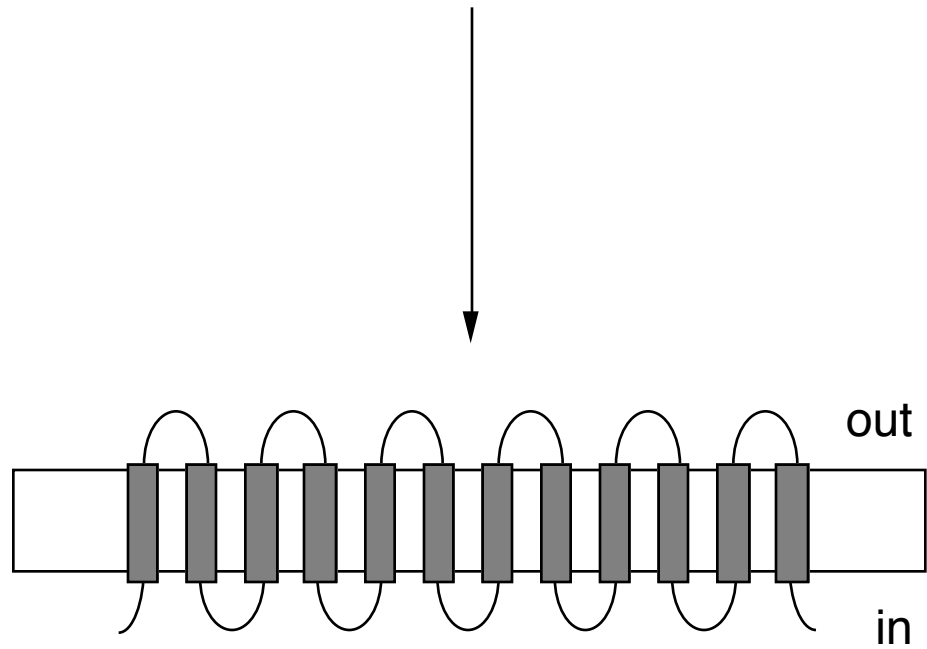


# Topology is controlled by positively charged residues

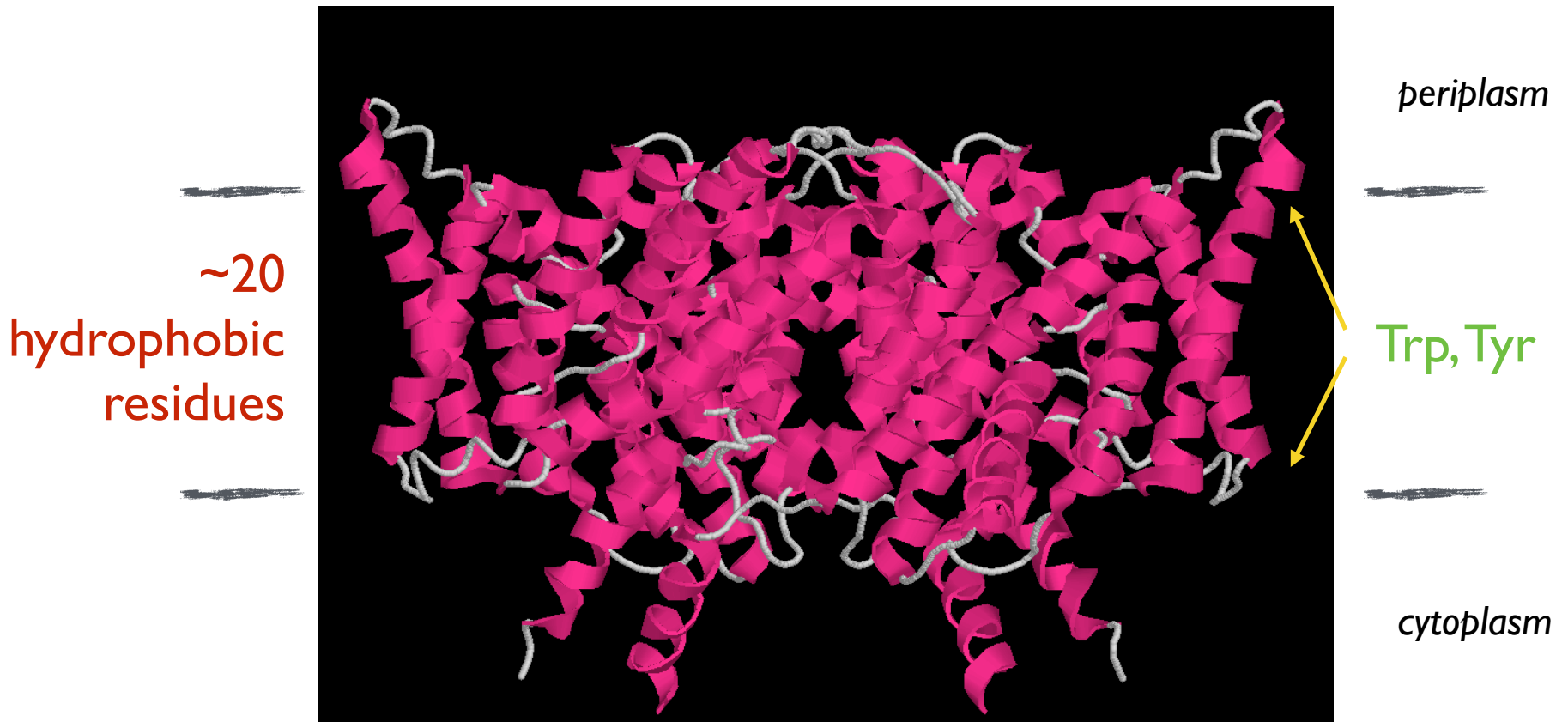


# Topology prediction

MDSQRNLLVIALLFVSFMIWQAW... ..

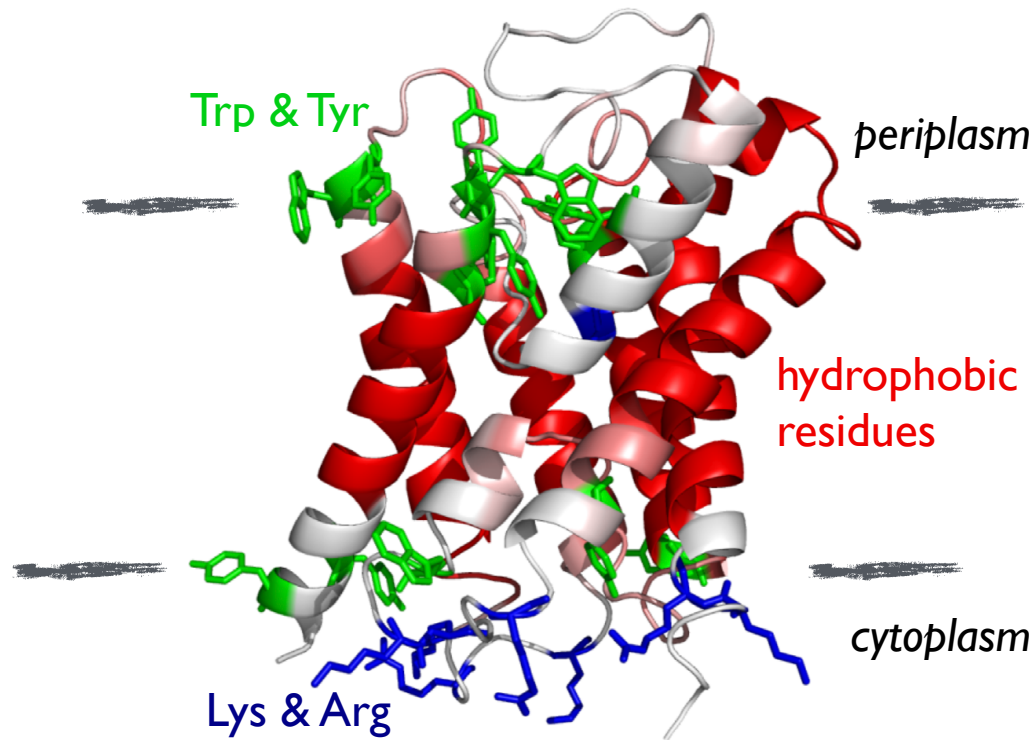


# The three most important characteristics



The positive-inside rule

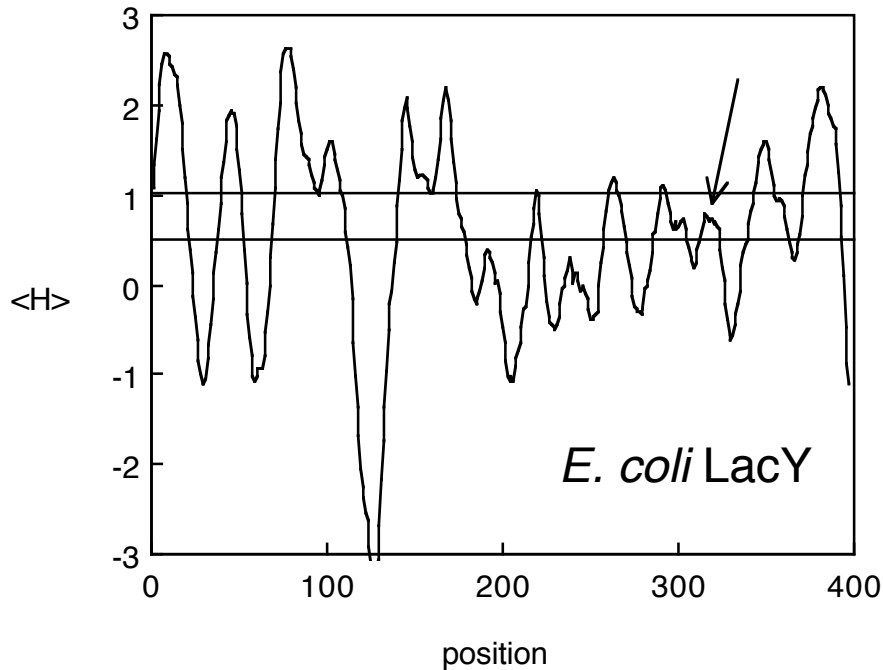
# The three most important characteristics



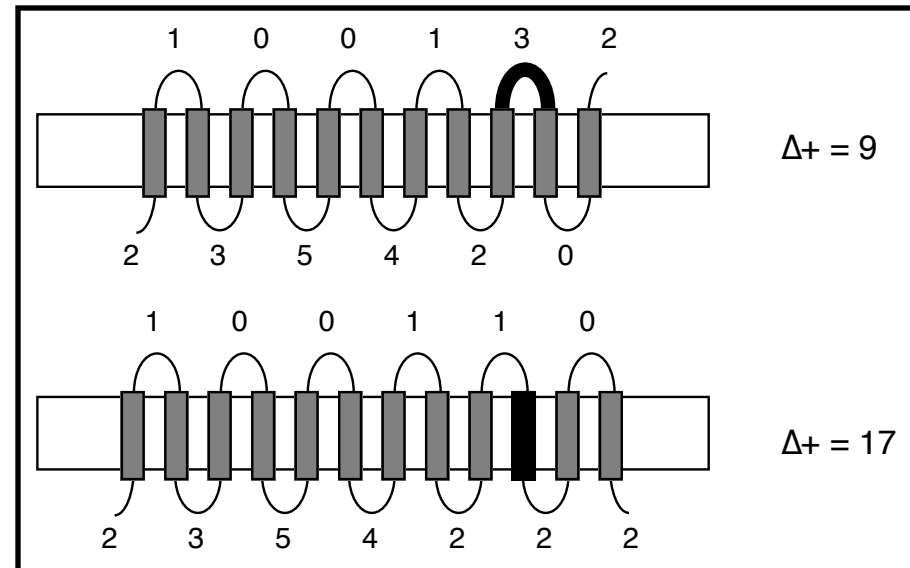
# Popular topology predictors

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)

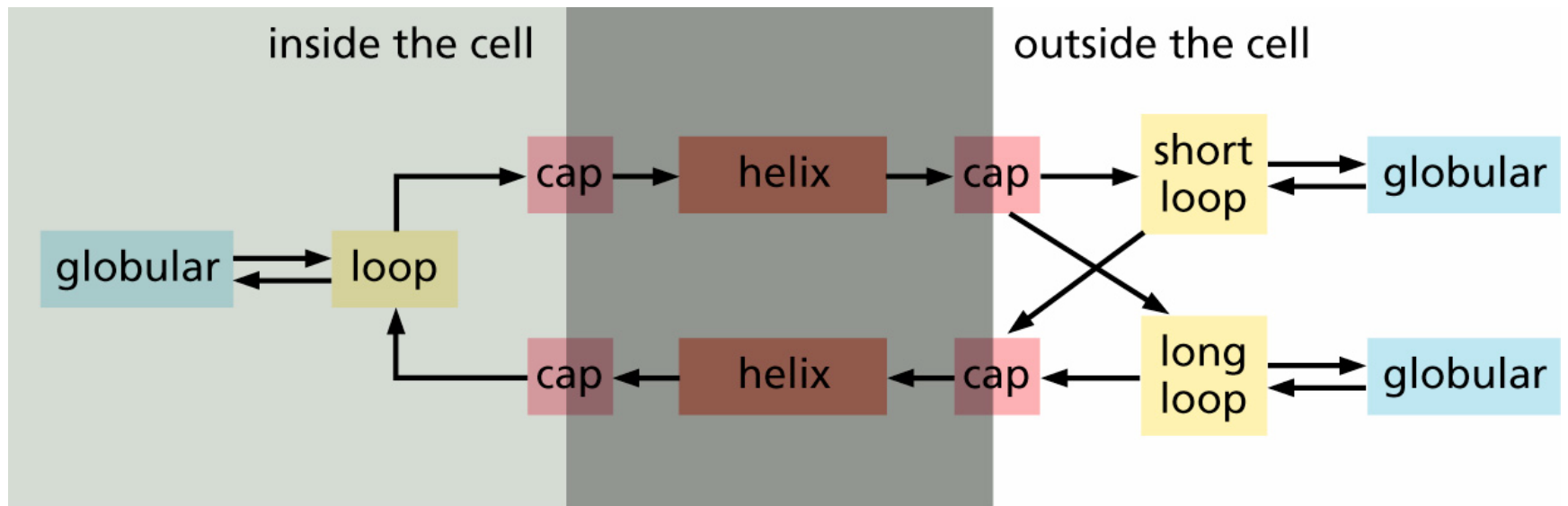
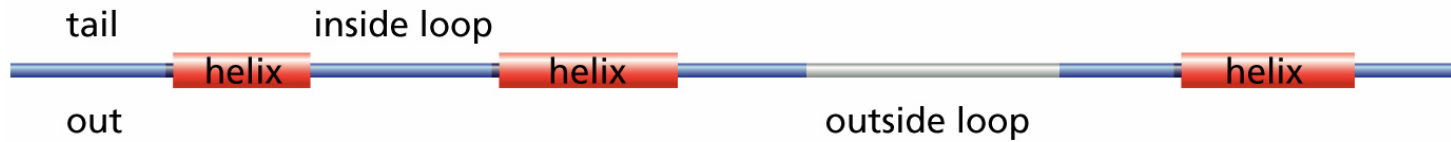
# TopPred



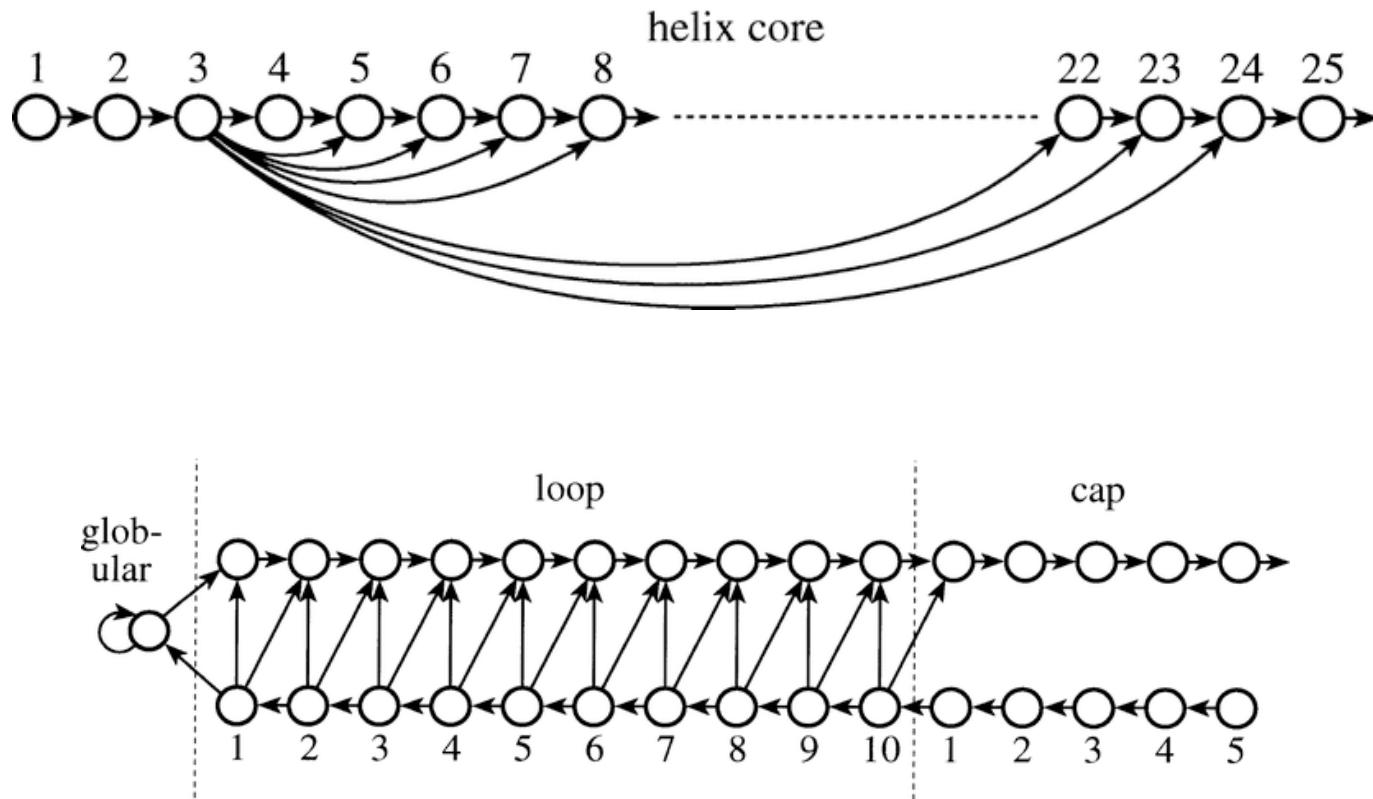
- construct all possible topologies
- rank based on  $\Delta+$



# TMHMM



# Helix and loop models in TMHMM



# TOPCONS

TOPCONS: Consensus prediction of membrane protein topology

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

DN.se - Nyheter Nyheter GvH 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** ▶

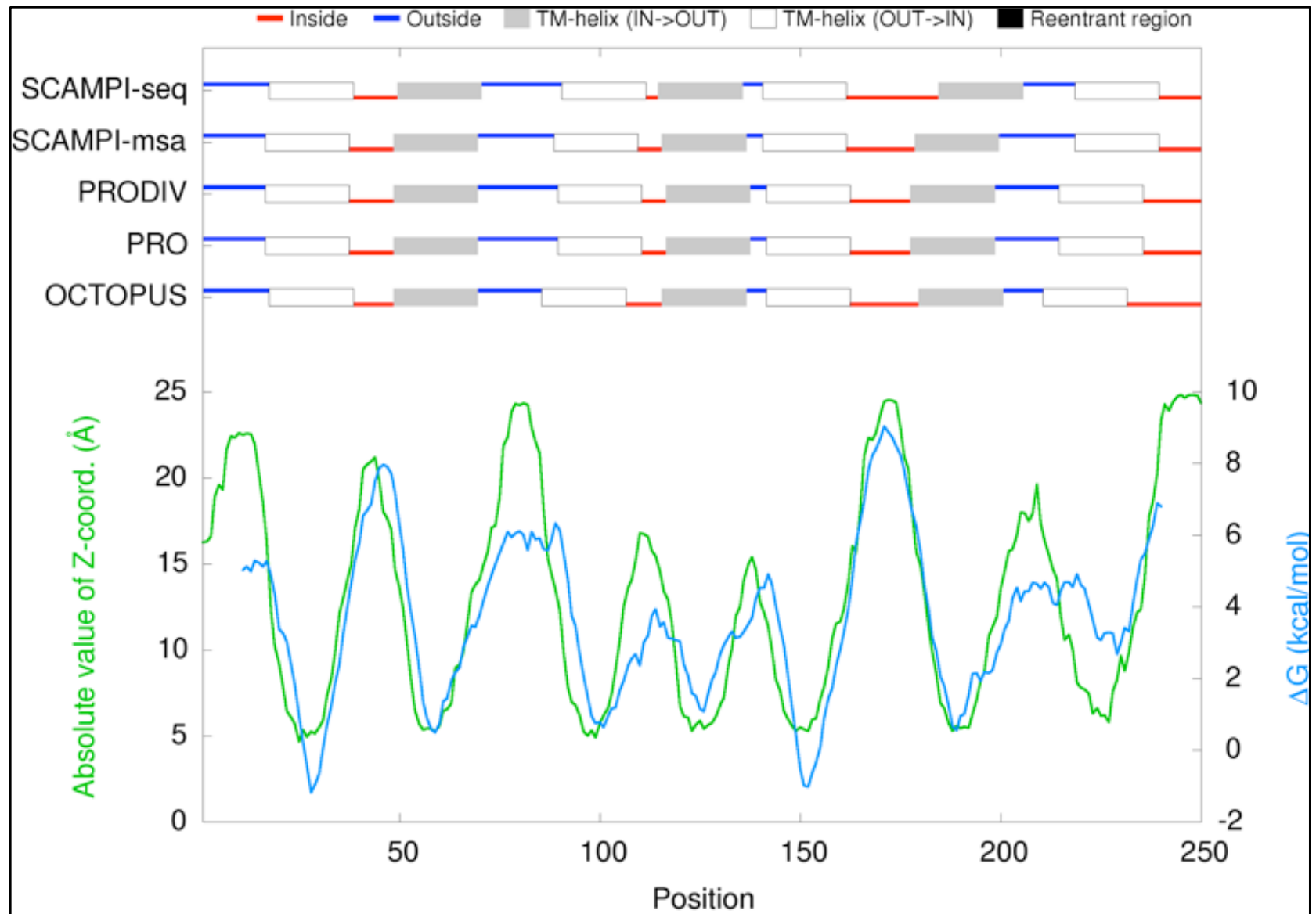
**References**

**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

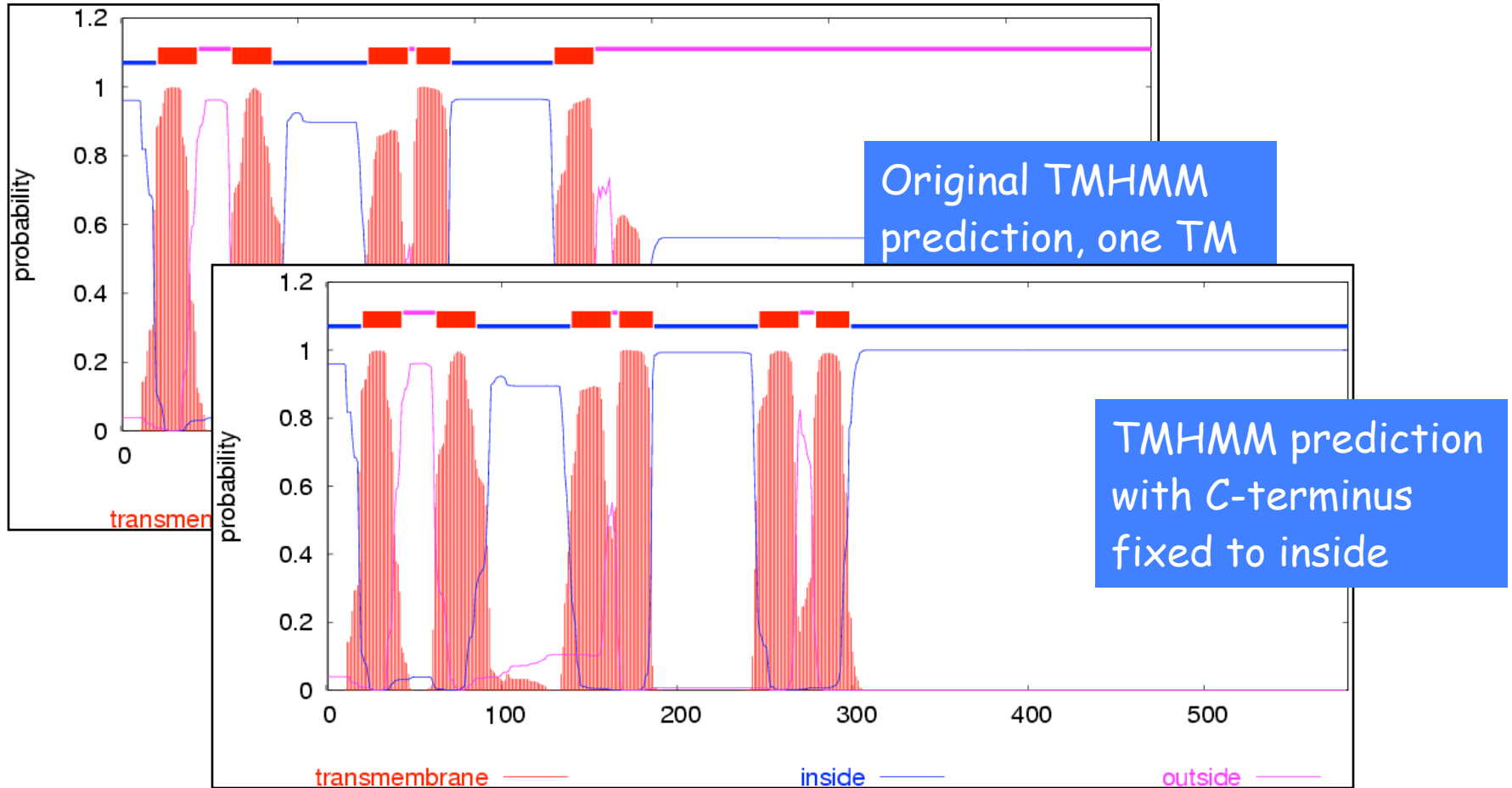


# How good are topology predictors?

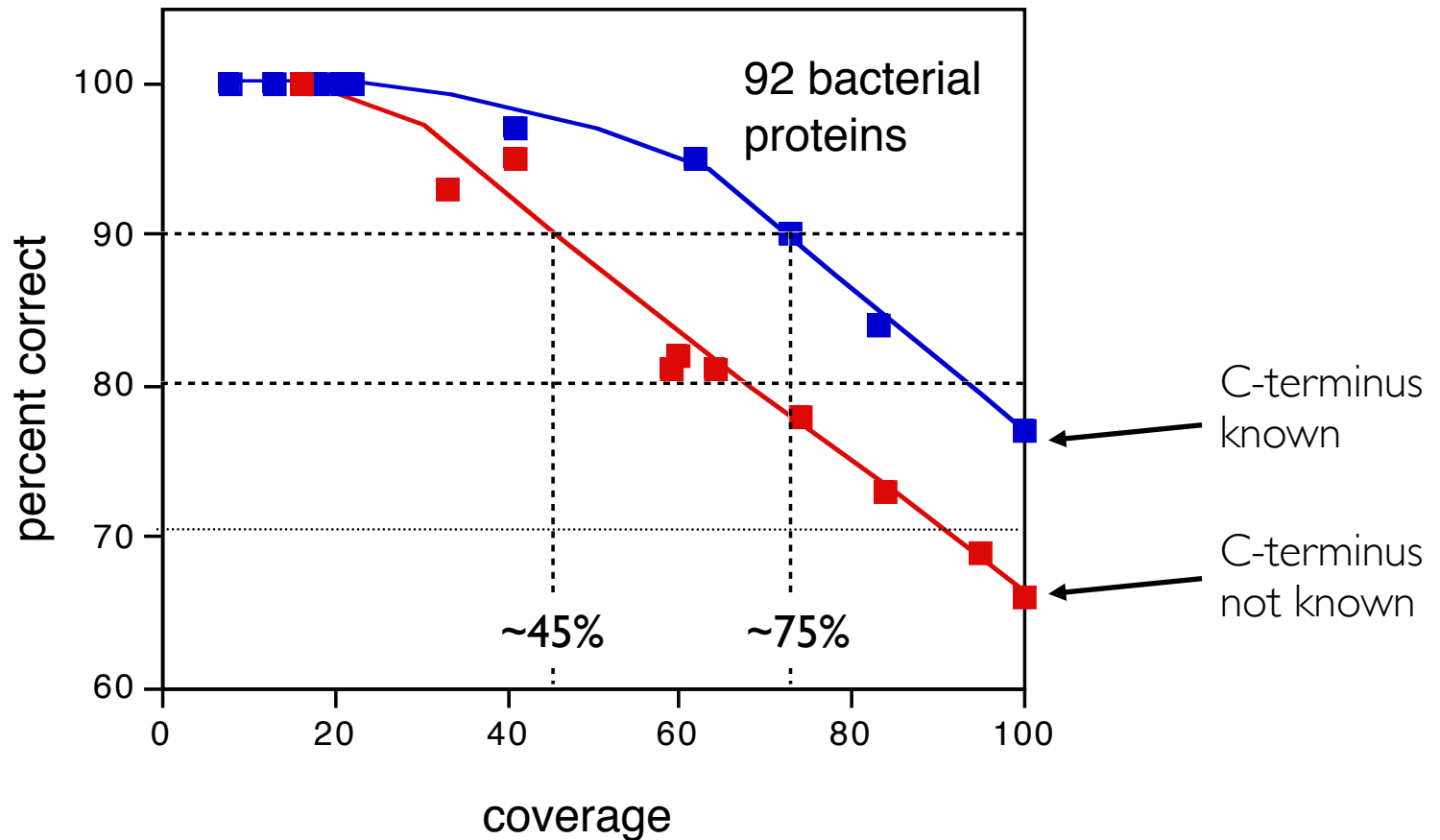
Discrimination membrane/soluble: sensitivity 97%; specificity 95%

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

# Experimental constraints help



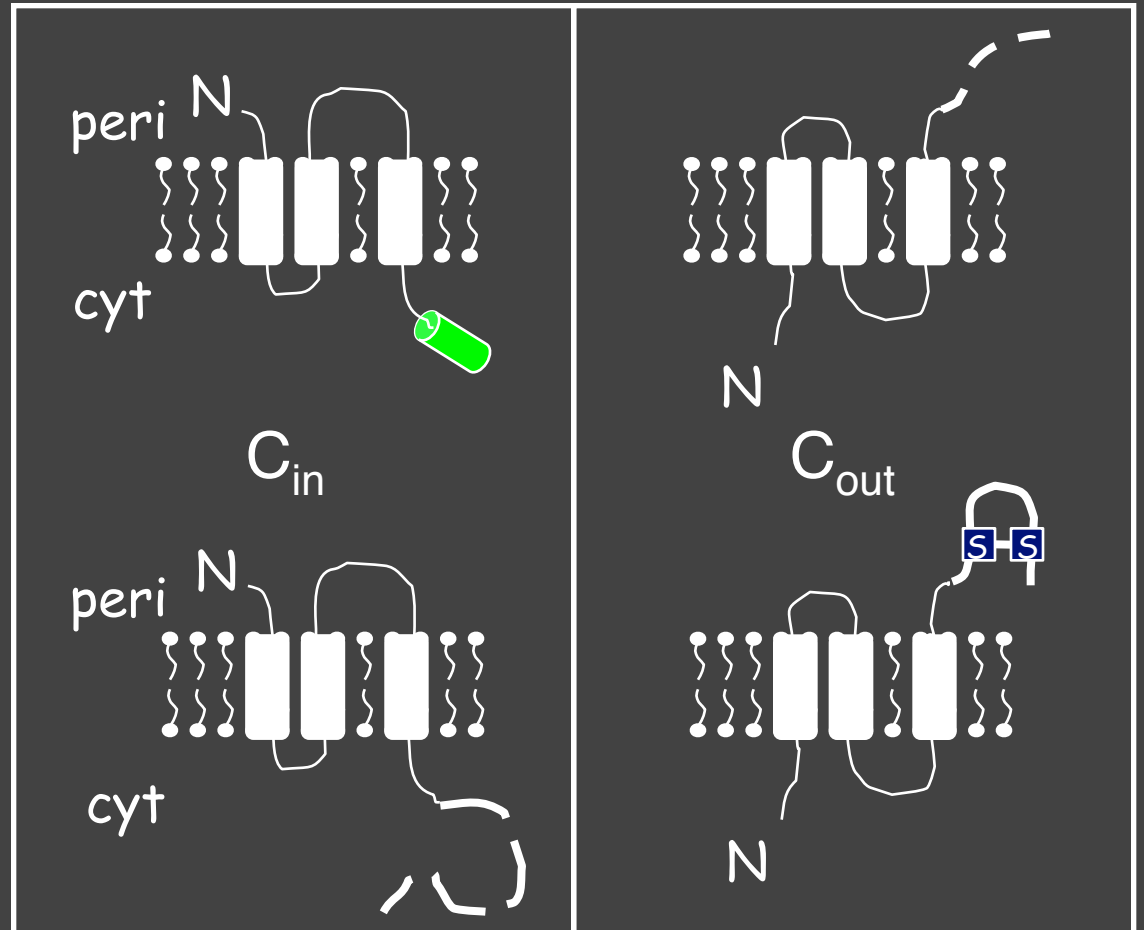
# Experimental constraints help



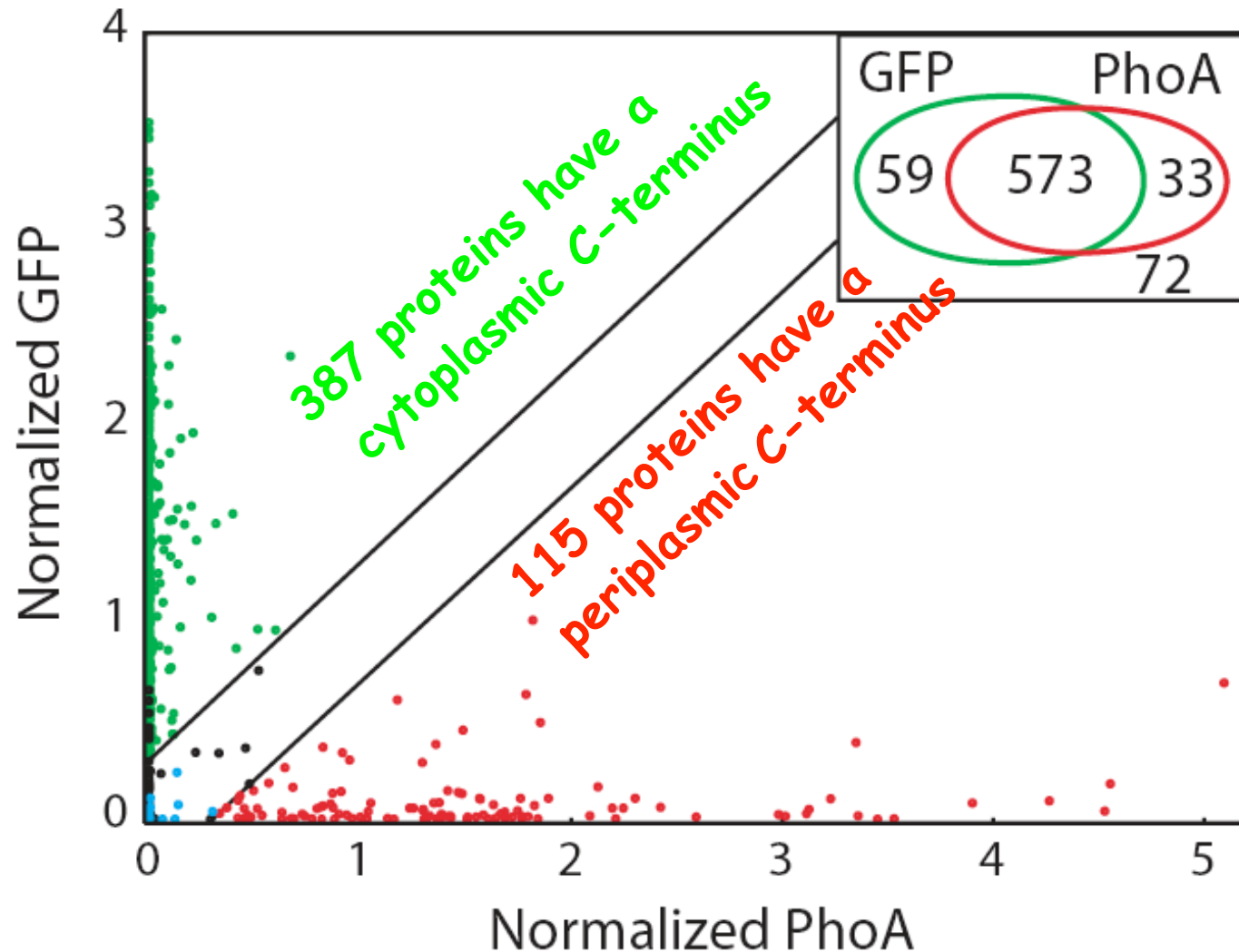
# Experimental constraints help

GFP is only active  
in the cytoplasm

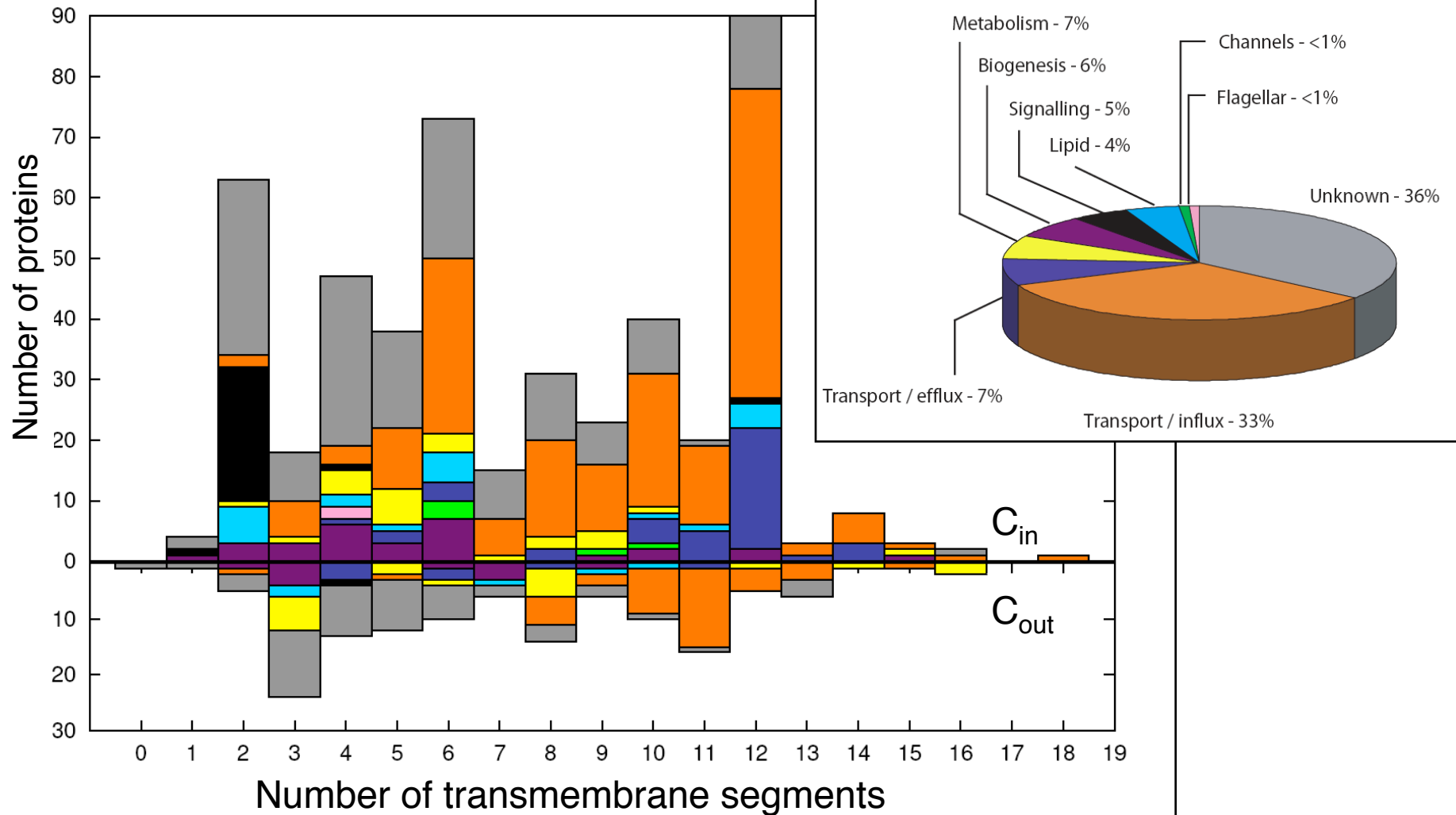
PhoA is only active  
in the periplasm



# Experimental constraints help



# Experimental constraints help

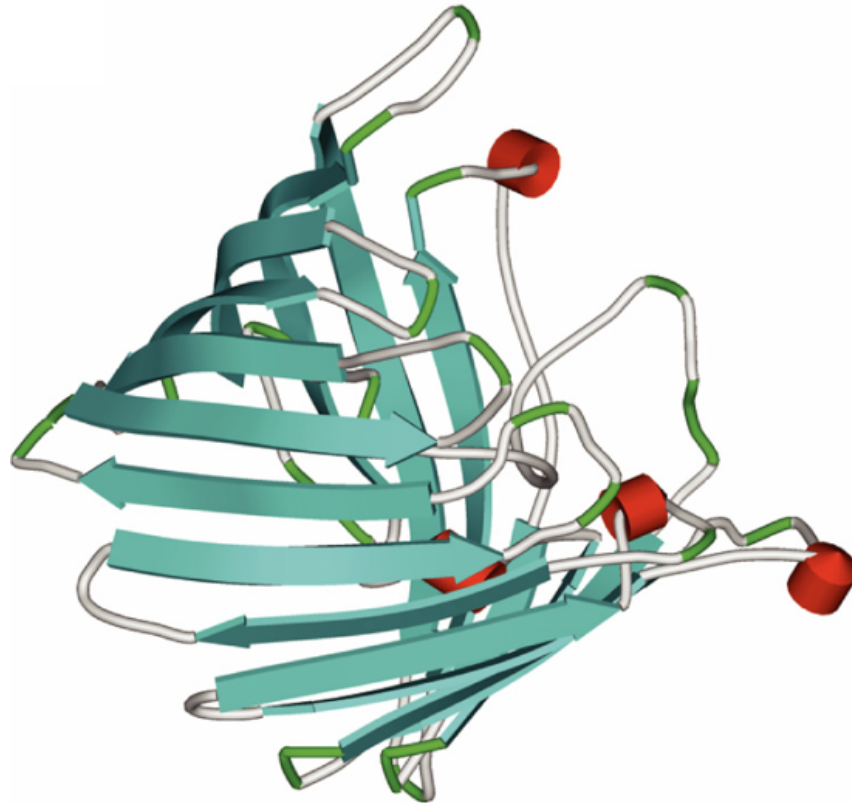


# ‘Exporting’ experimental constraints using alignments

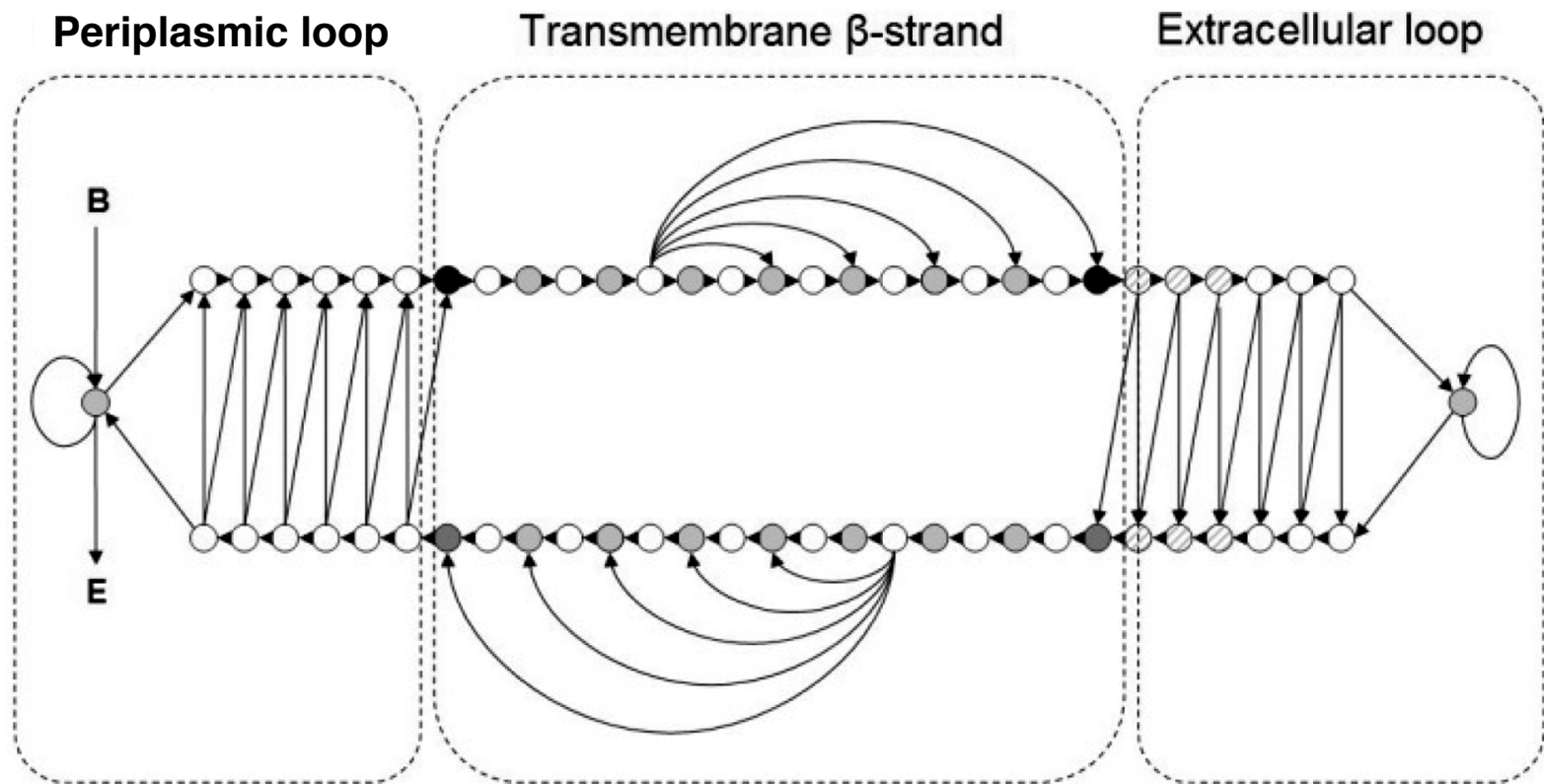


225/38 bacterial/eukaryotic genomes  
158 k/139 k predicted membrane proteins  
51.000/15.000 assignments

# Topology prediction for $\beta$ -barrel membrane proteins



# PRED-TMBB2: An HMM method for $\beta$ -barrel membrane proteins



# Don't forget...

Two architectures: helix bundle and  $\beta$ -barrel

Hydrophobic transmembrane helices

Alternating Hyf-X  $\beta$ -strands

The positive-inside rule

TopPred

TMHMM

TOPCONS

PRED-TMBB2

Experimental constraints help