Structure and function of proteins

1. Amino acids and peptides

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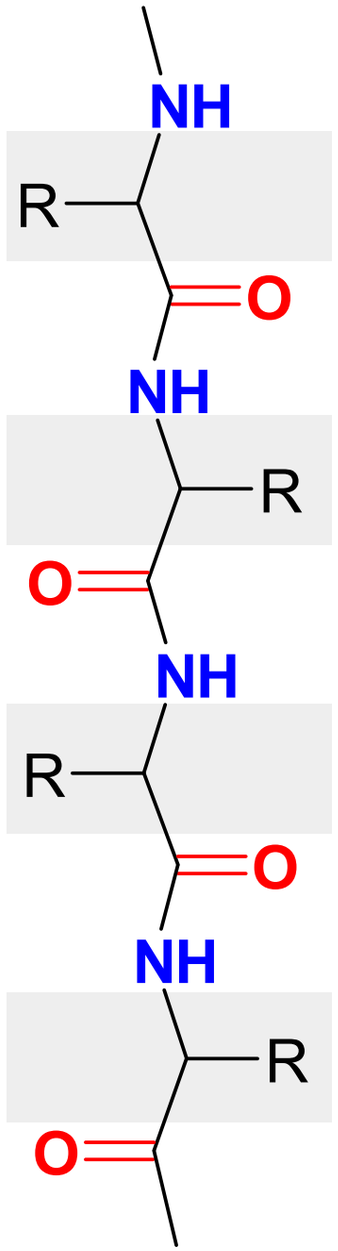
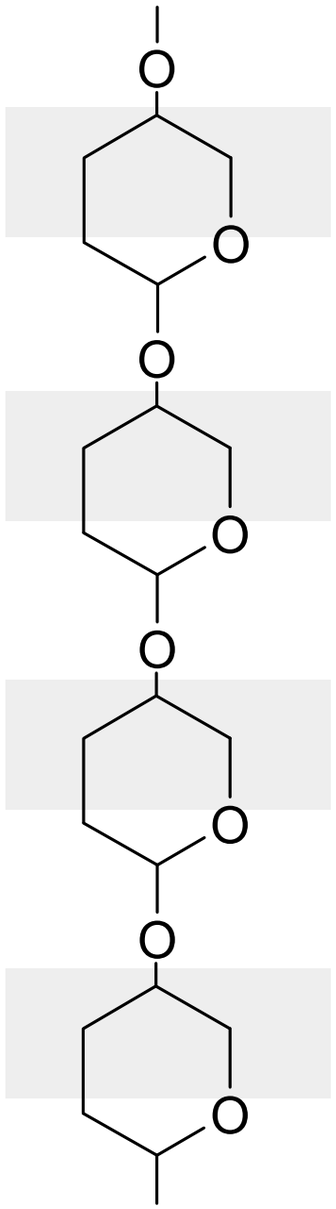
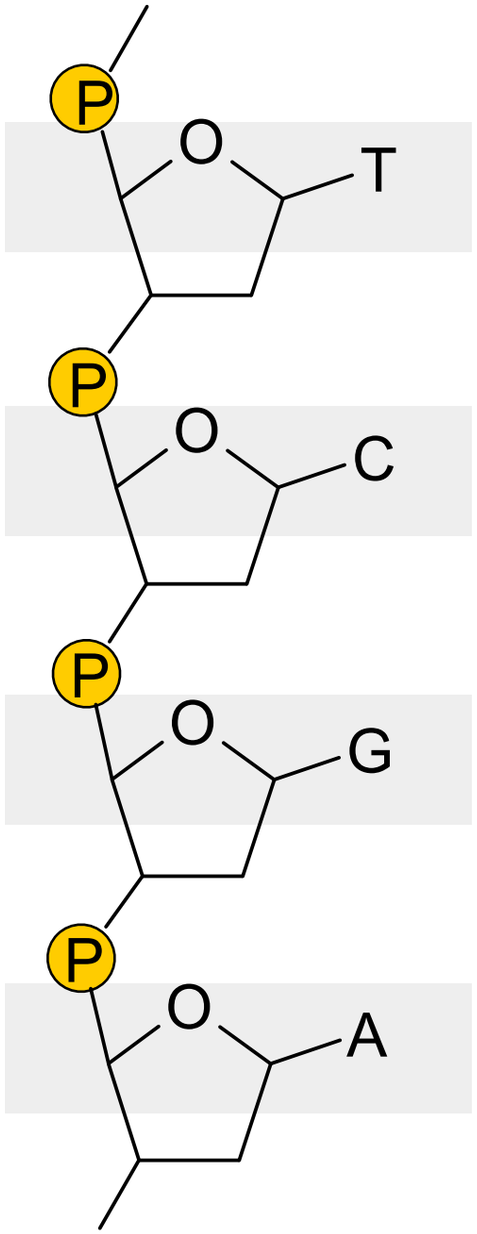
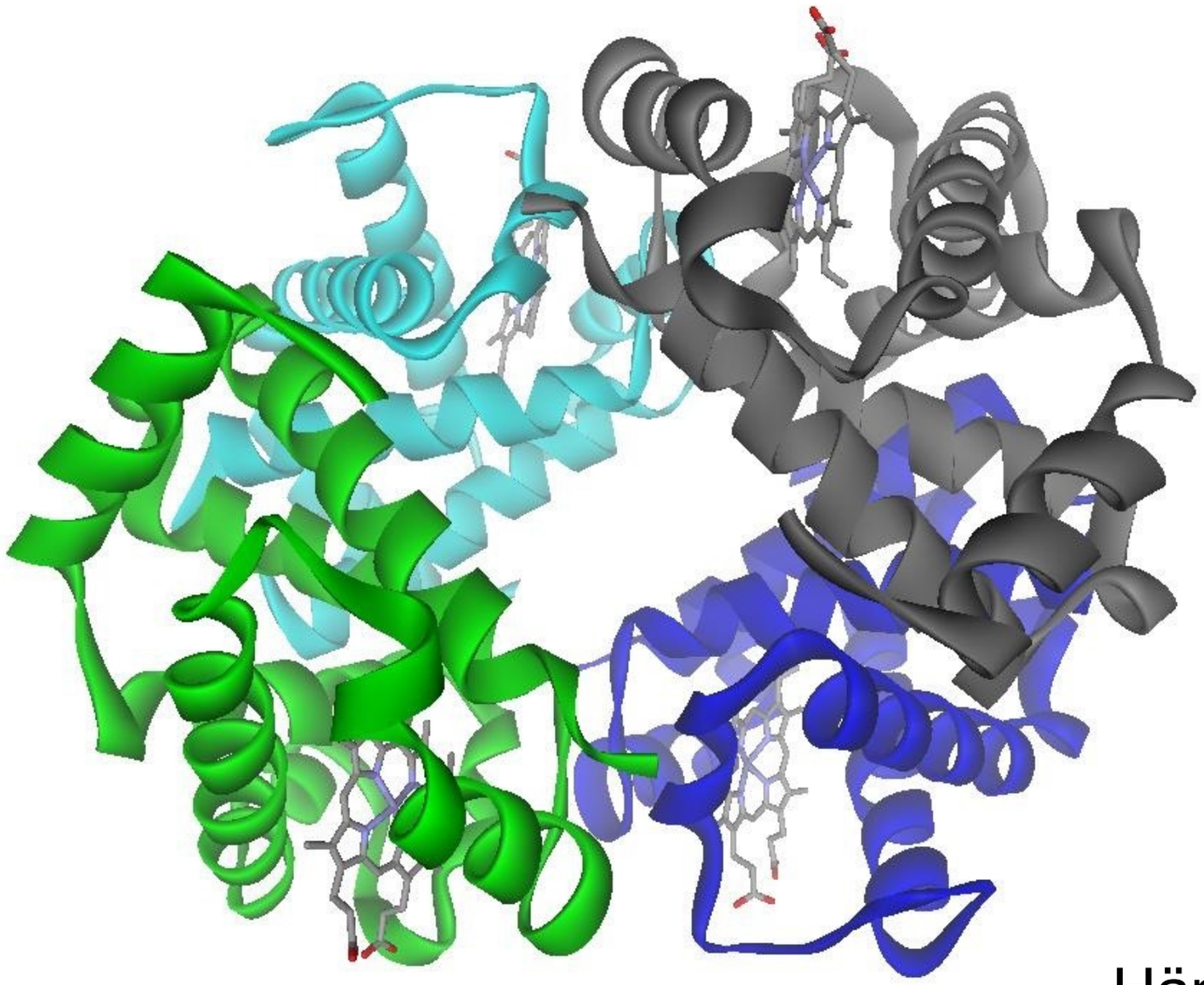
Institut für Medizinische Physik und Biophysik
Universität Leipzig

Biopolymers:	Proteins	Polysaccharids	DNA/RNA
			
Building blocks:	Amino acids	Mono saccharids	Nucleotide
bonding:	Peptide bond (=Amid)	O-glycosidic bond	Phosphoric acid -diester

Proteins

The properties of amino acids determine the tertiary structure of proteins



Hämoglobin

Proteinogenic amino acids

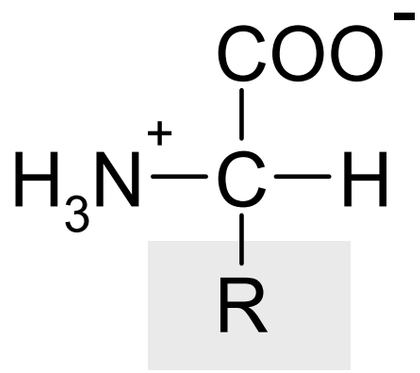
amino acids	3-letter -code	1-letter -code
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartate	Asp	D
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamate	Glu	E
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I

amino acid	3-letter -code	1-letter -code
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

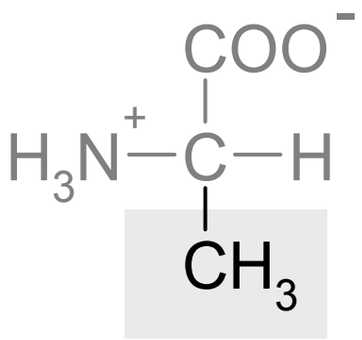
Classification of amino acids

- Necessity to take in by food
  - essential
  - semi-essential (depending on age and period of growth)
  - non-essential

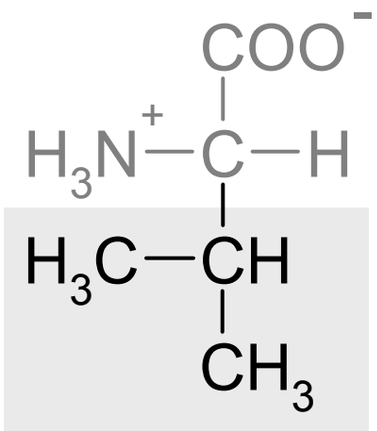
- Property of side chain:
  - non polar (hydrophobic)
  - aromatic
  - polar, uncharged
  - basic
  - acidic



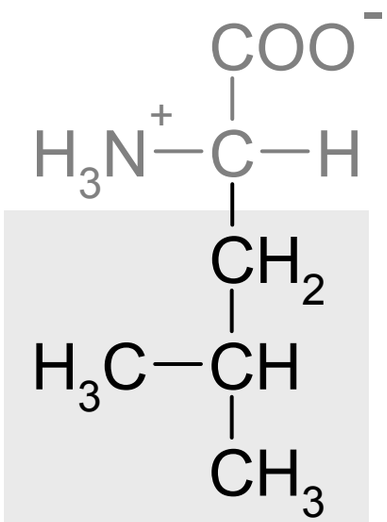
Amino acids with <u>non polar</u> side chains



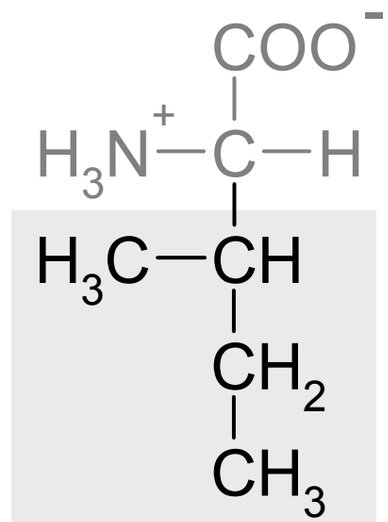
Alanine



Valine

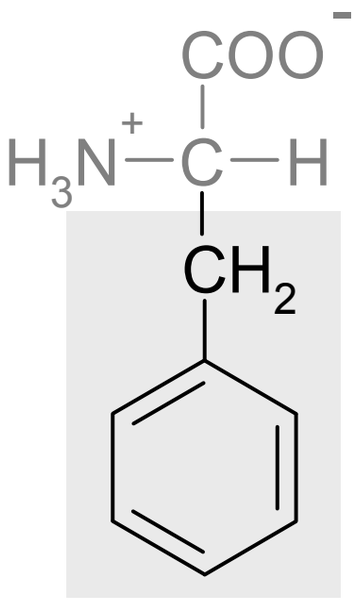


Leucine

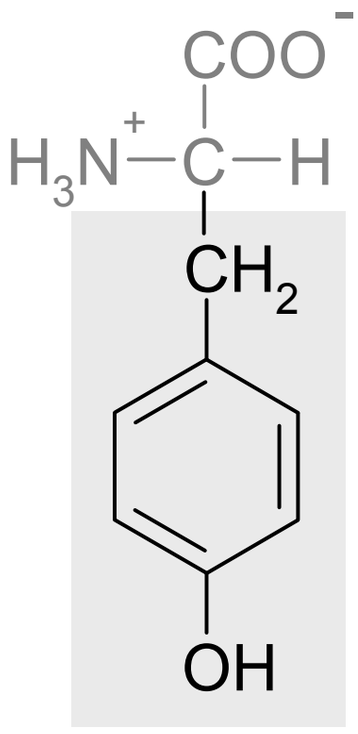


Isoleucine

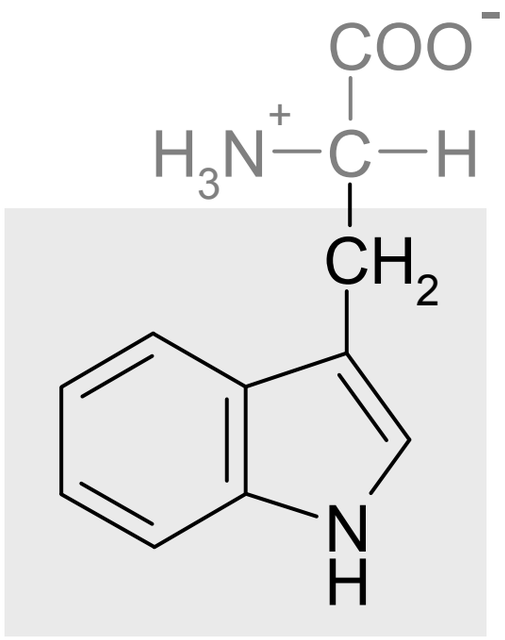
Amino acid with <u>aromatic</u> Side chains



Phenylalanine



Tyrosine



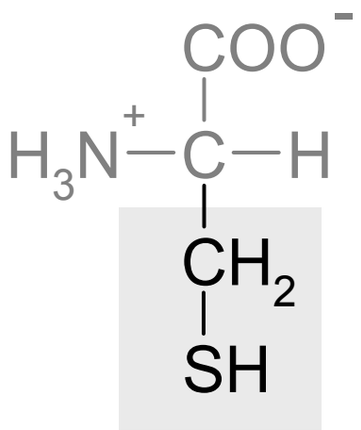
Tryptophan

Proteins

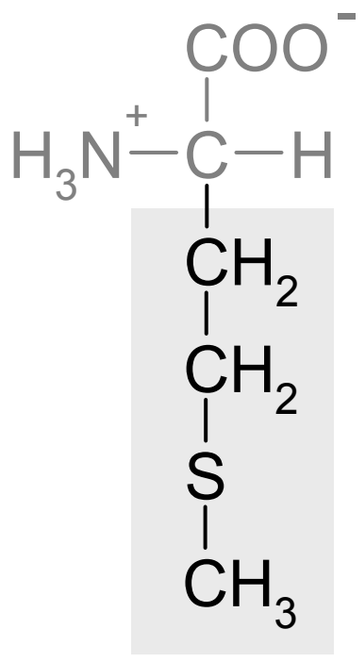
Amino acids with non polar / aromatic side chains are hydrophobic:

- Stabilization of protein structures by hydrophobic interactions
- Anchoring of proteins in membranes
- building hydrophobic binding pockets for hydrophic substrates

Sulphureous amino acids



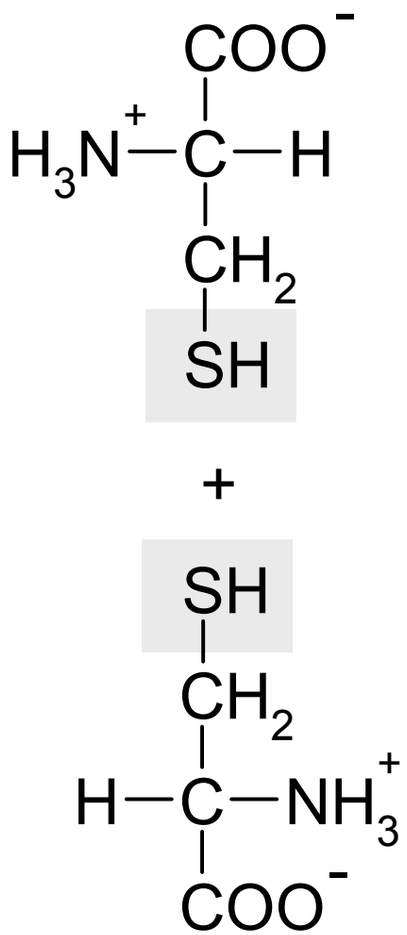
Cysteine



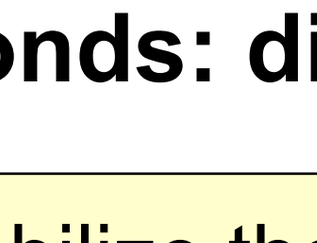
Methionine

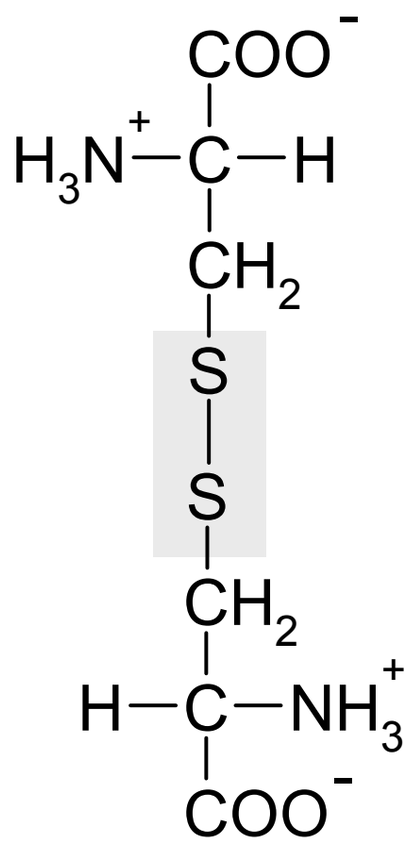
Covalent bonds: disulfide bridges

Disulfide bridges stabilize the tertiary structure of peptides and proteins



2 x Cysteine

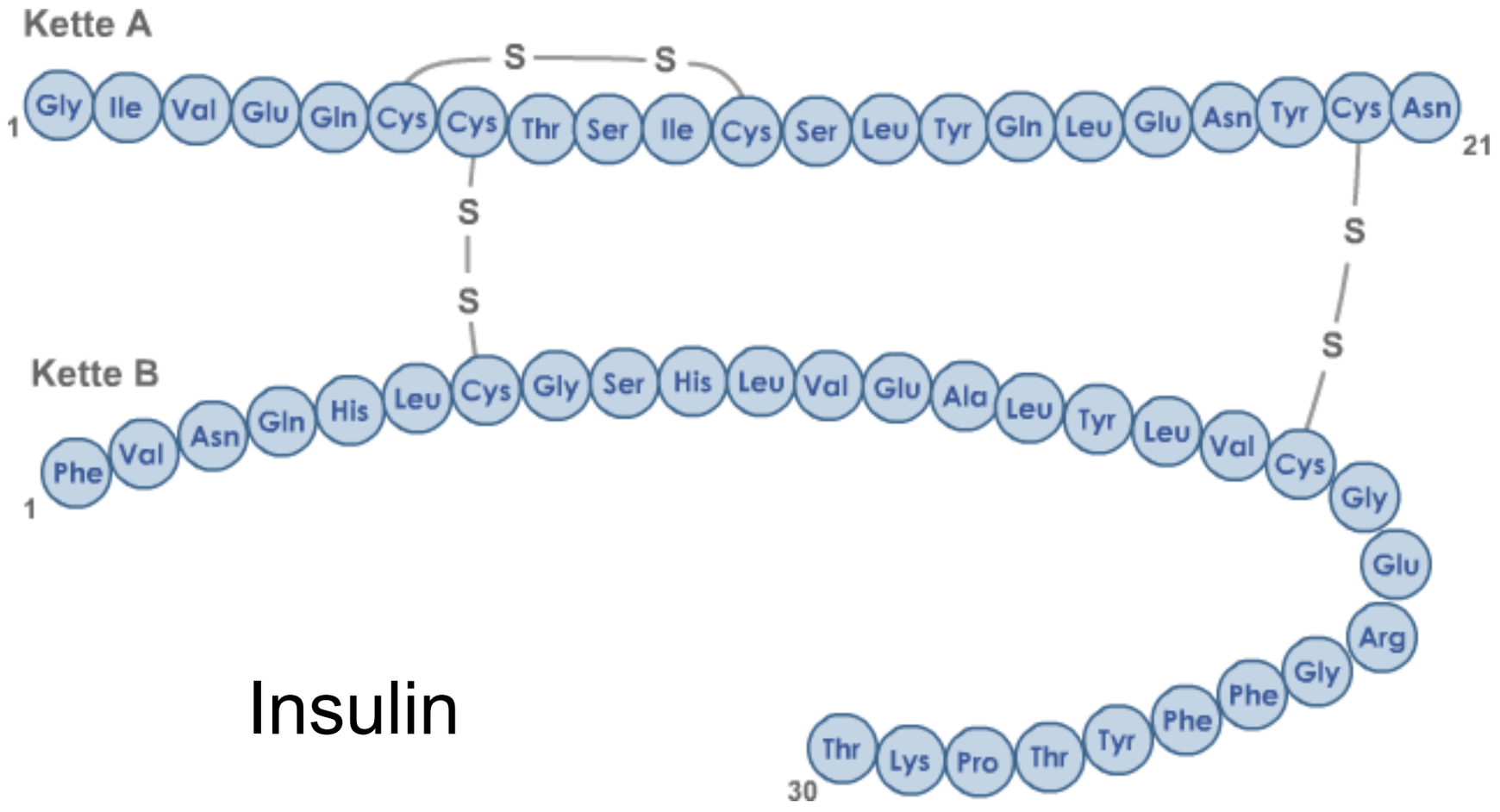




Cysteine
(disulfide bridge)

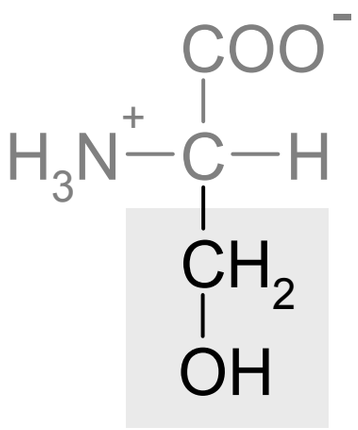
covalent bonds: disulfide bridge

Disulfide bridges stabilize the tertiary structure of peptides and proteins

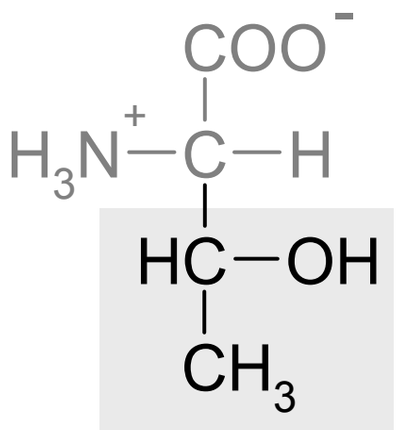


Insulin

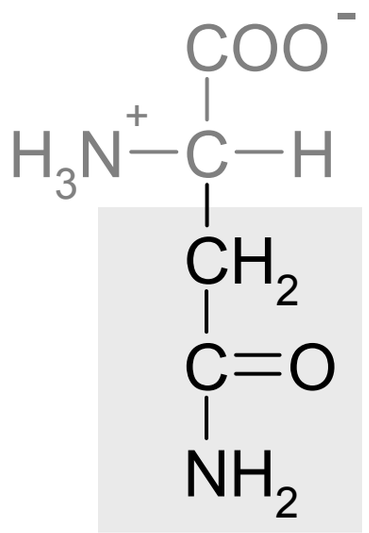
Amino acids with <u>polar</u>, <u>uncharged</u> side chains



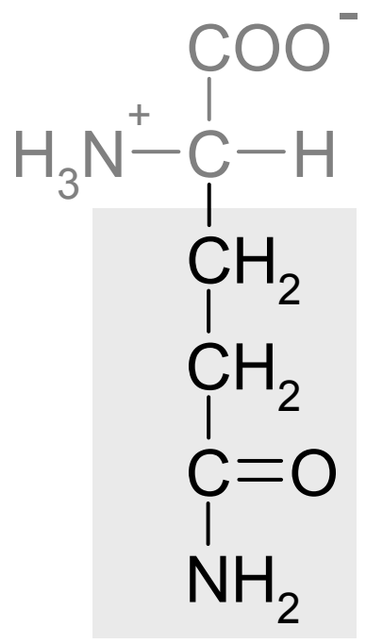
Serine



Threonine

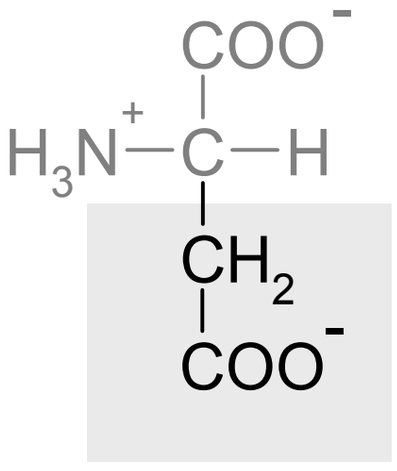


Asparagine

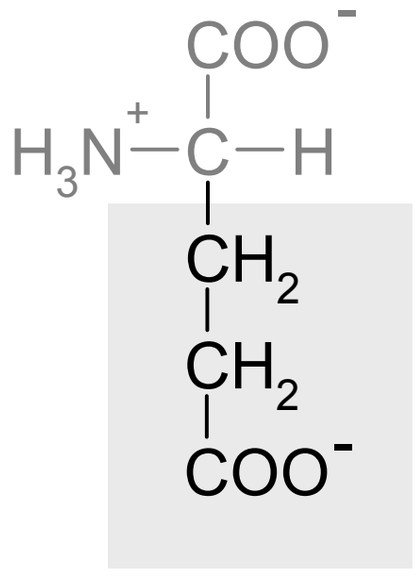


Glutamine

Amino acids with acidic side chains

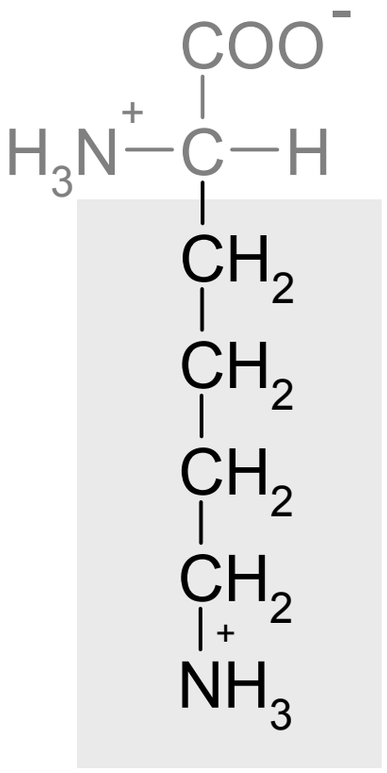


Aspartate
(Aspartic acid)

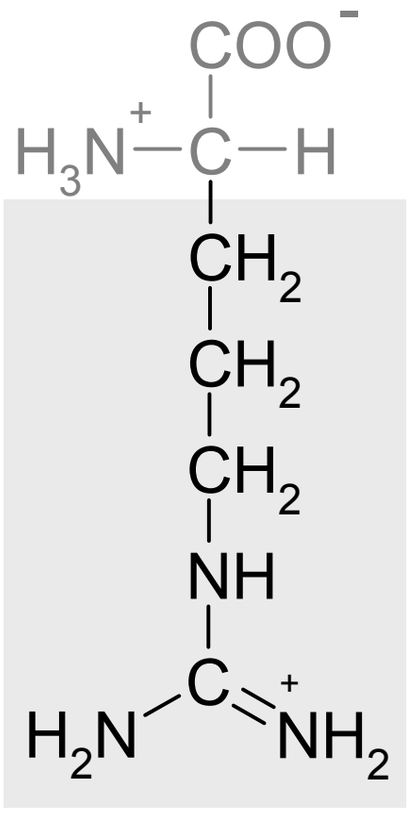


Glutamate
(Glutamic acid)

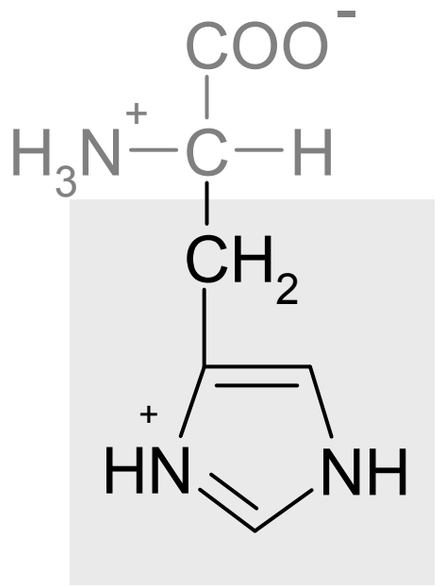
Amino acid with <u>alkaline side chain</u>



Lysine



Arginine

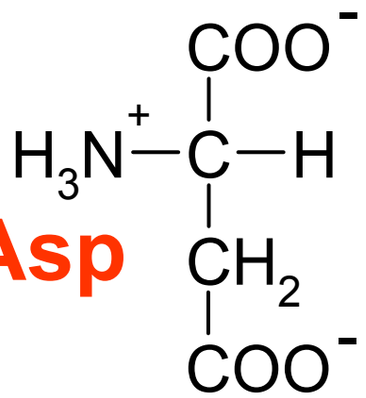


Histidine

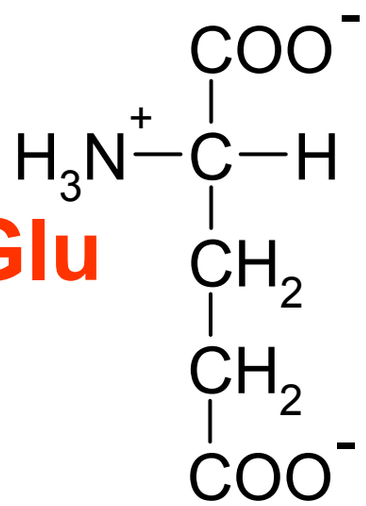
Acidic and alkaline amino acids:

which form predominates at pH = 7?

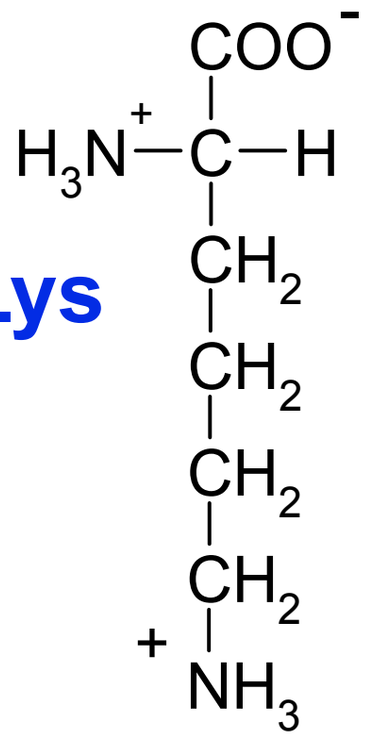
Asp



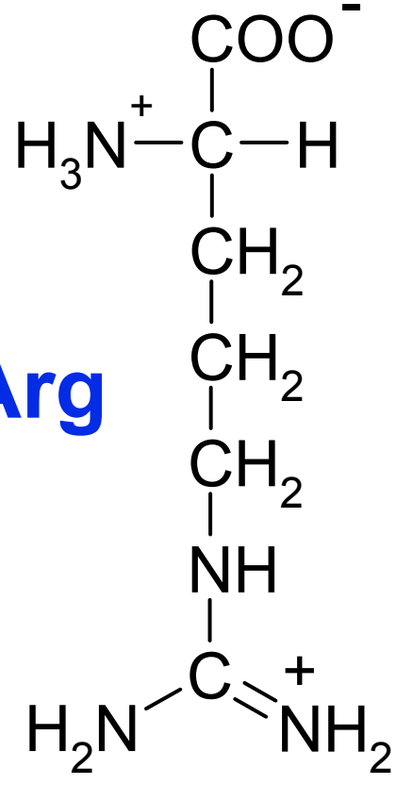
Glu

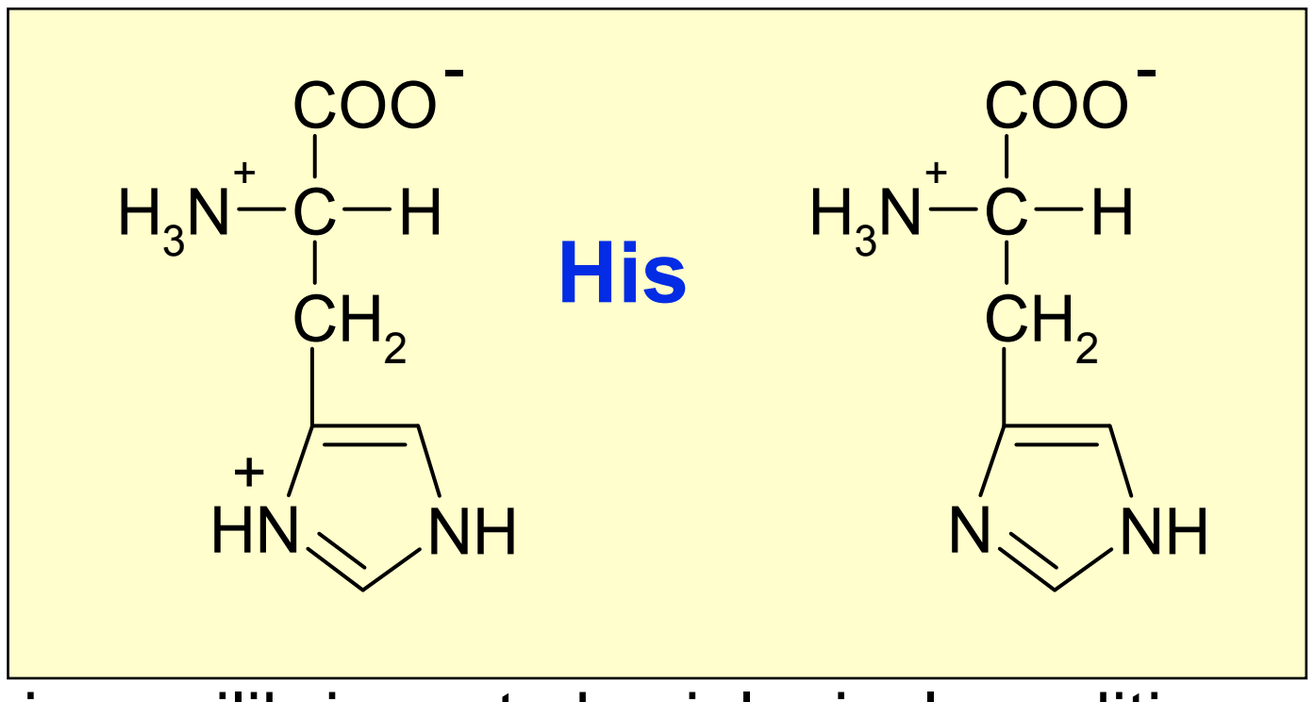


Lys



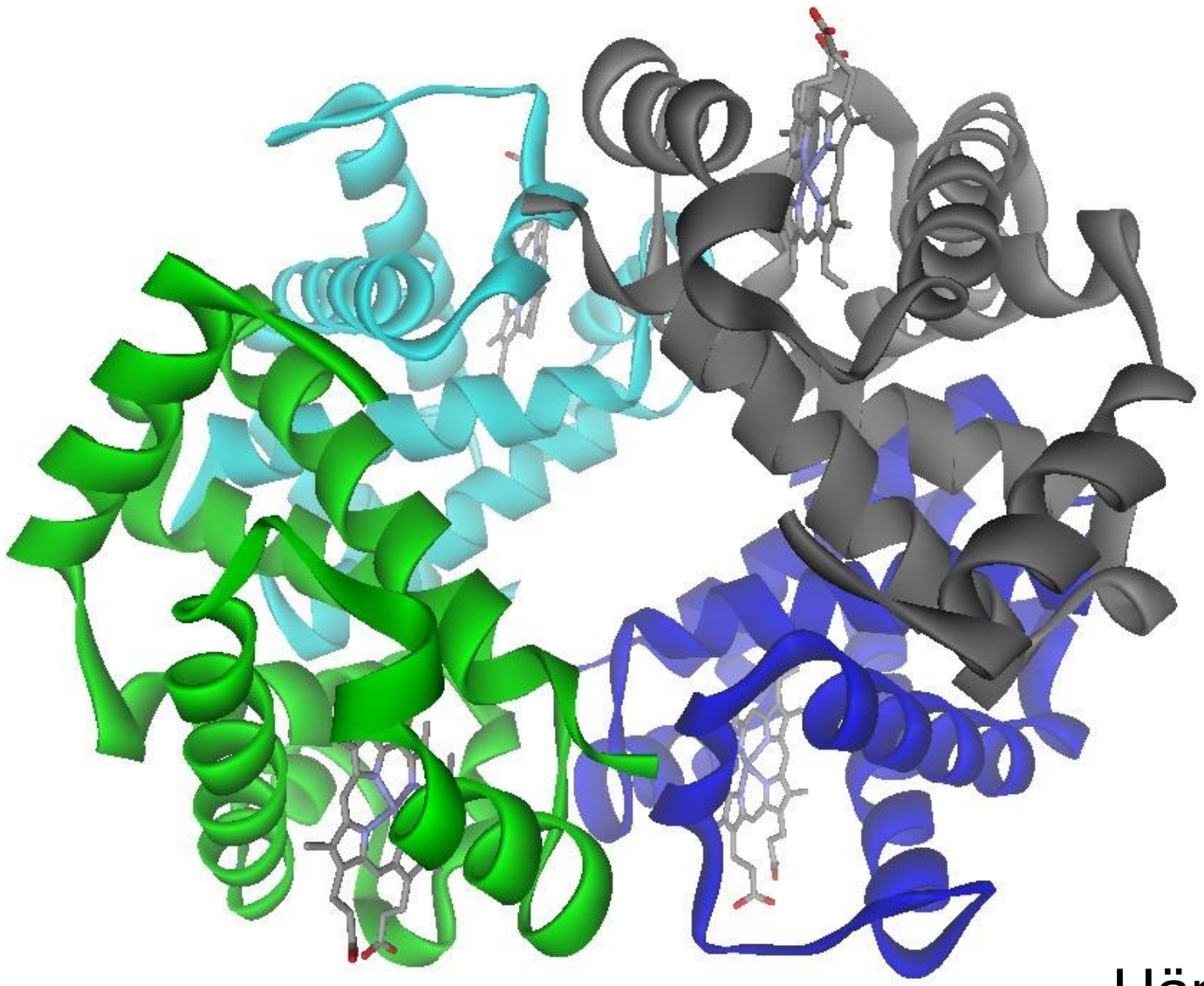
Arg





in equilibrium at physiological conditions

The properties of amino acids determine the tertiary structure of proteins



Hämoglobin

Proteins

Amino acids with <u>polar, uncharged</u> side chains
Side chains are hydrophilic:

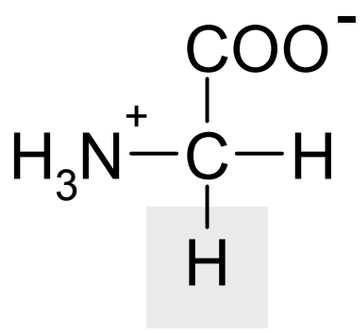
- Tertiary structure stabilisation of proteins by hydration

- by hydrogen bonds

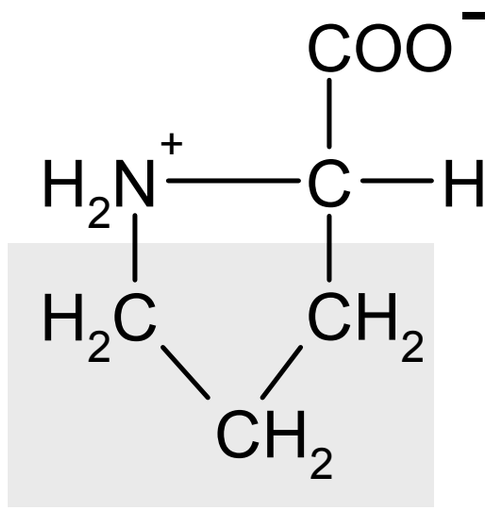
- by salt bridges

- Formation of hydrophilic binding pockets for hydrophilic substrates

Special amino acids



Glycin



Prolin

-’destabilize secondary structures (proline termintes alpha helices

-induce tertiary structure flexibility

Structure and function of proteins

2. Proteins

Prof. Dr. Peter Hildebrand

Institut für Medizinische Physik und Biophysik
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Proteines

Function	Example
Catalysis (enzyme)	Hexokinase (Phosphorelates glycose)
Structuring	Collagen (connective tissues; Knochen)
Transport	Hemoglobin (transport in blood)
Storage	Ferritin (Fe storage in liver)
Mobility	Actin/Myosin (muscle)
Immune system	Antibodies
Signal transmission	β-Adrenergic receptor
Pores/Channels/Carrier	Na^+-Ion channel; Glucose-Carrier
Growth control	Growth factors

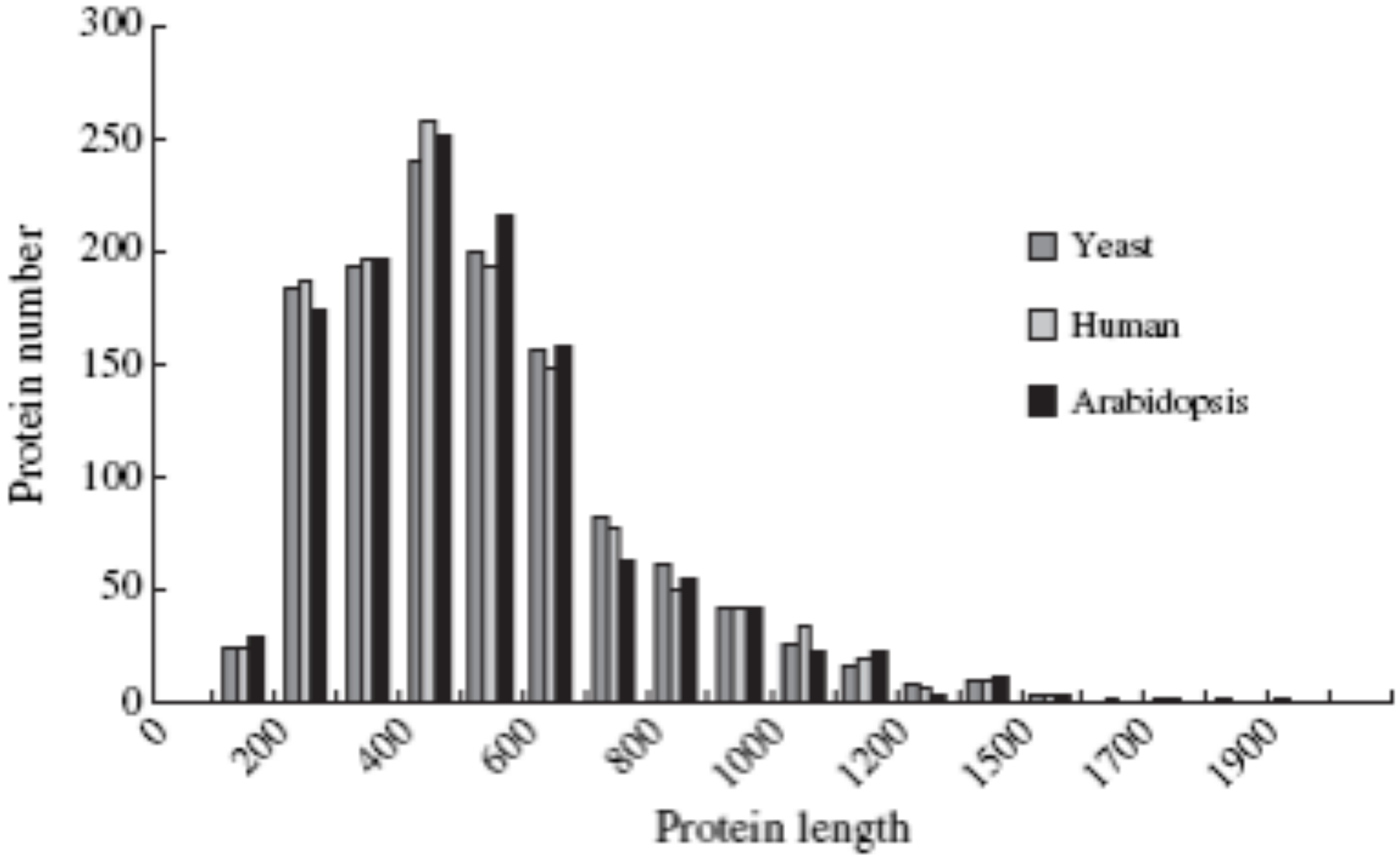
Peptide and protein

Classification by amino acid number
(more or less arbitrary):
Peptide, oligo-peptide, poly-peptide, proteine

Number of
amino acids:

5	Encephaline (Neuropeptide: pain)
9	Oxytocin (hormone: contraction of)
84	Pro-insulin (precursor of insuline)
153	Myoglobin (O2 storage of muscle)
ca. 2000	Myosine (musle filament)
ca. 30.000	Titin (molekular "Fether" of muscle)

How big are proteins?

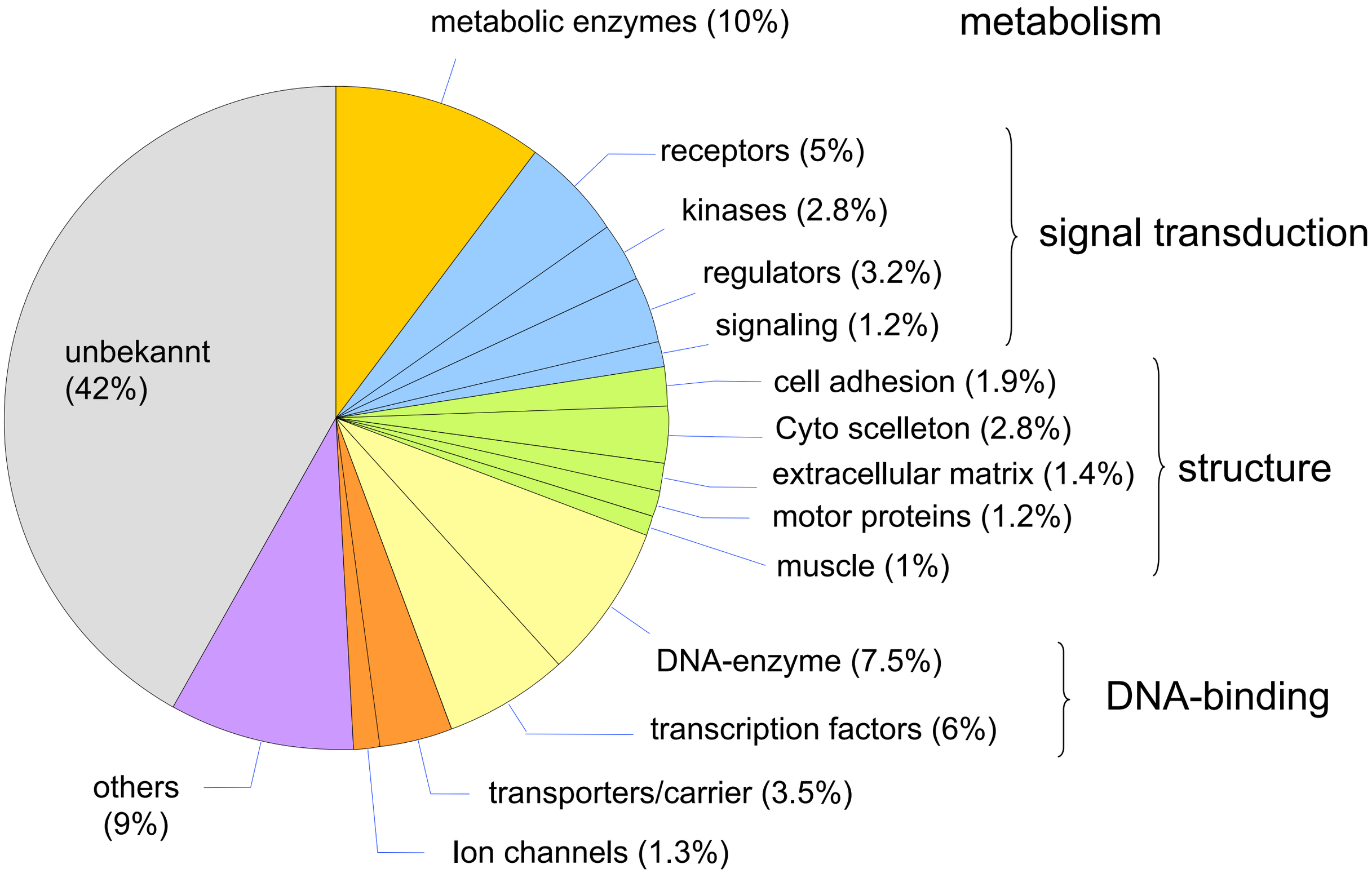


How many proteins are there?

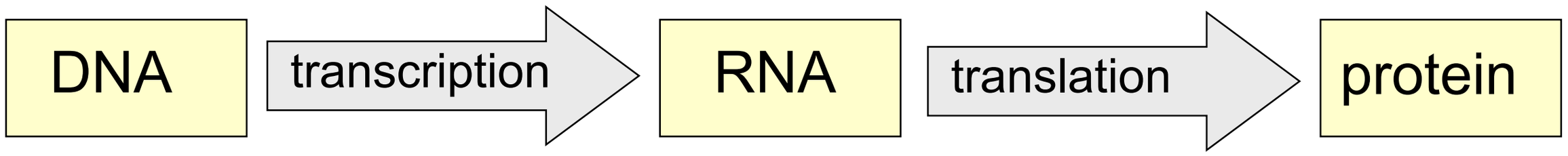
Organism	Proteine
AIDS-virus	18
Escherichia coli	2.300
Drosophila	ca. 13.600
Homo sapiens	ca. 100.000

Distribution of the molecular function of 26,383 human genes

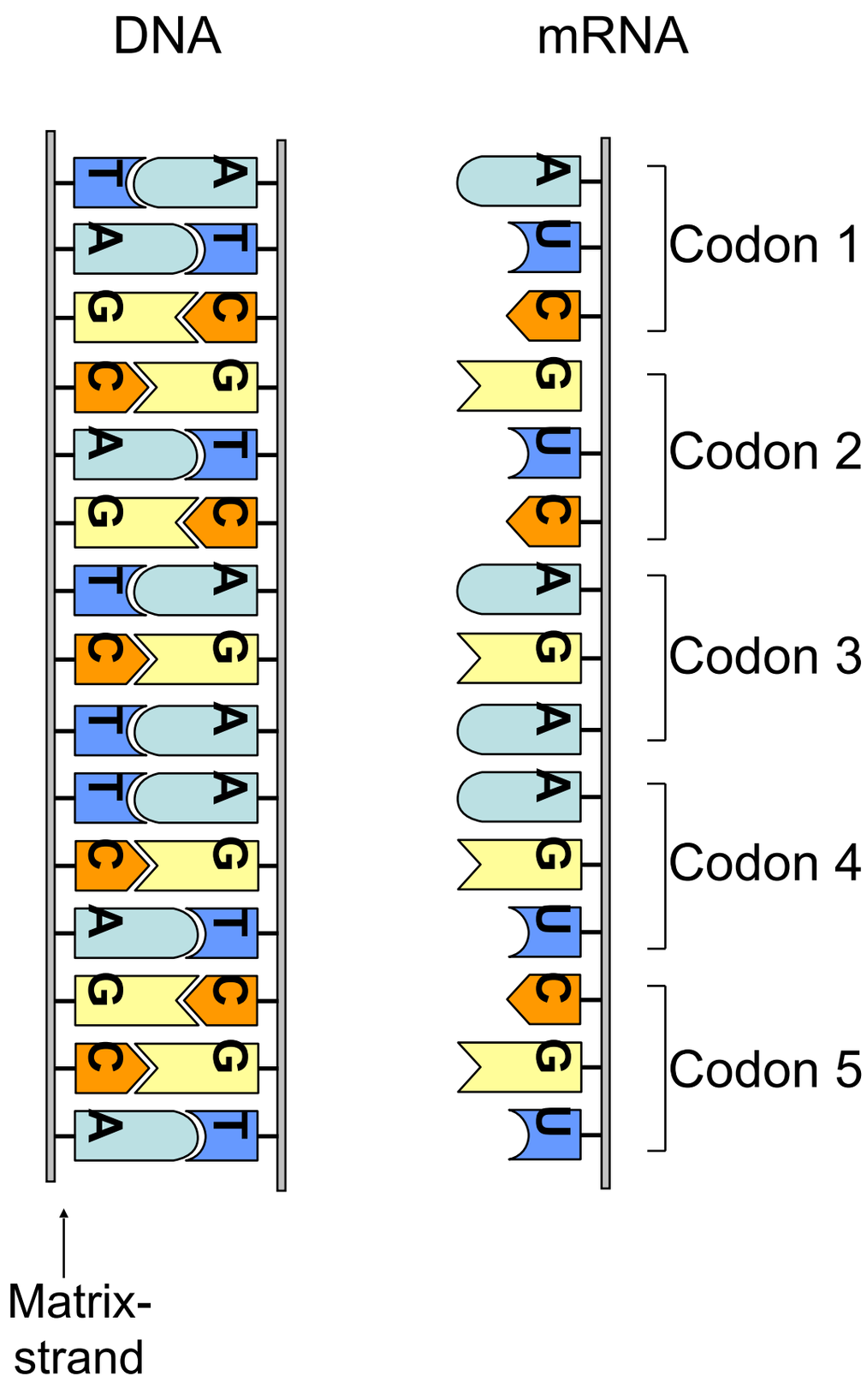
adapted from Venter et al. (2001) Science 291, 1304 -1351



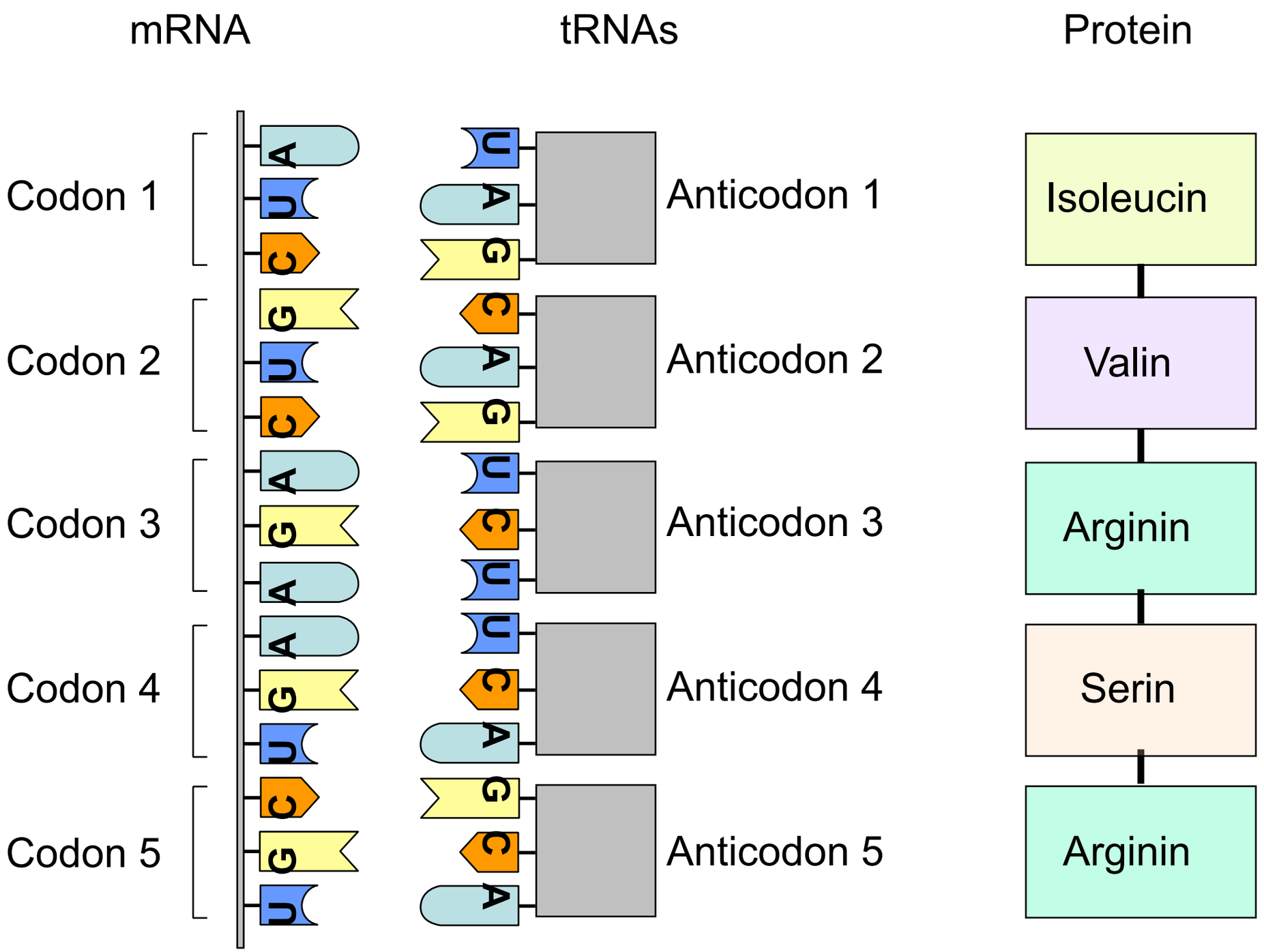
Central dogma of molecular biology



Genetical Code

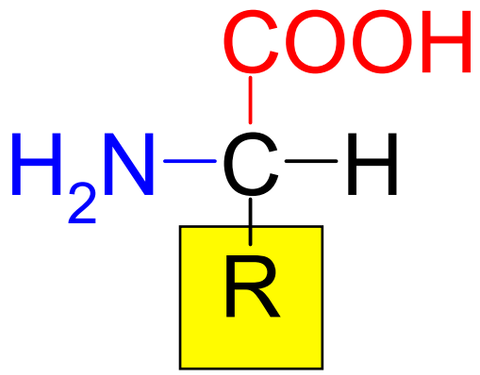


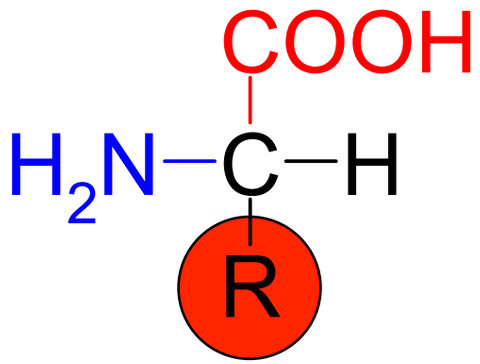
Genetical Code

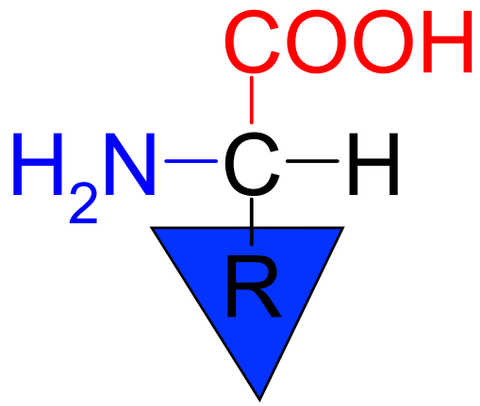


Amino acids

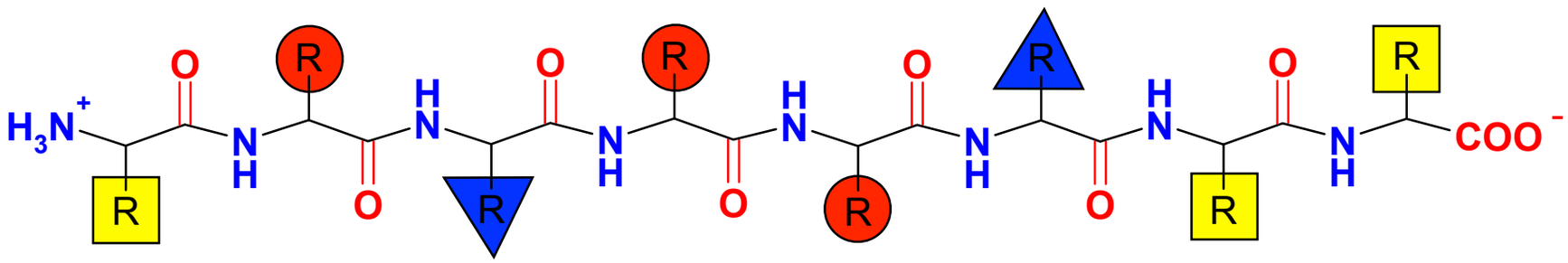
Amino acids are connected through peptide bonds to poly peptides and proteins





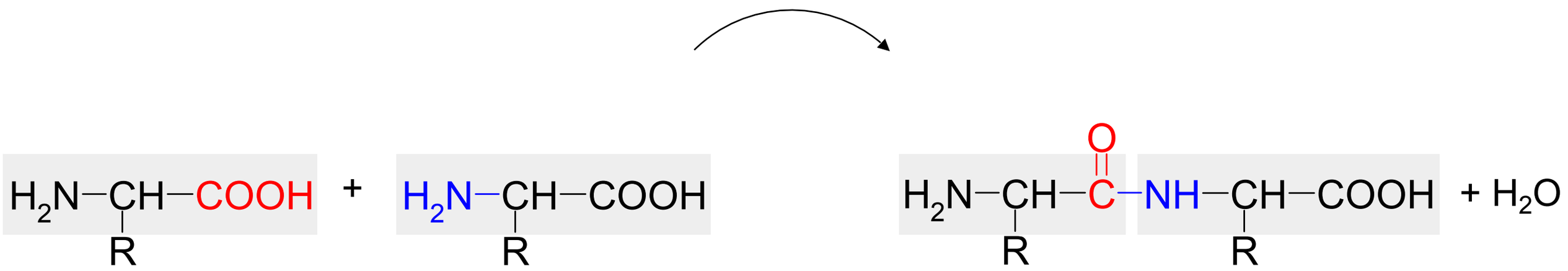


Protein



Peptide bond

Built at the Ribosom
(need of energy: ATP)



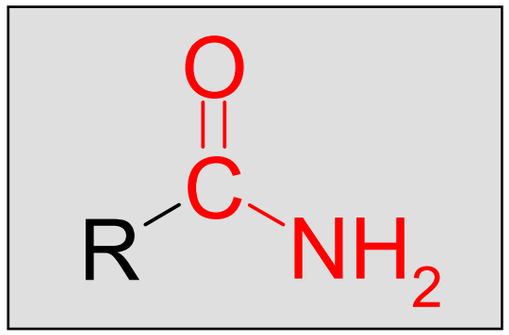
Amino acid

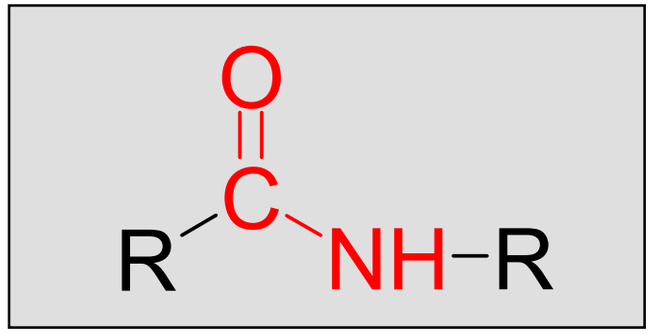
Amino acid

Peptide

Hydrolysis with help of enzymes
(proteases)

Amide





Amide:

- from carbon acids und amines
- can be hydrolyzed
- forms hydrogen bonds
- partially double bond of the C-N bond (mesomerie)
- neutral

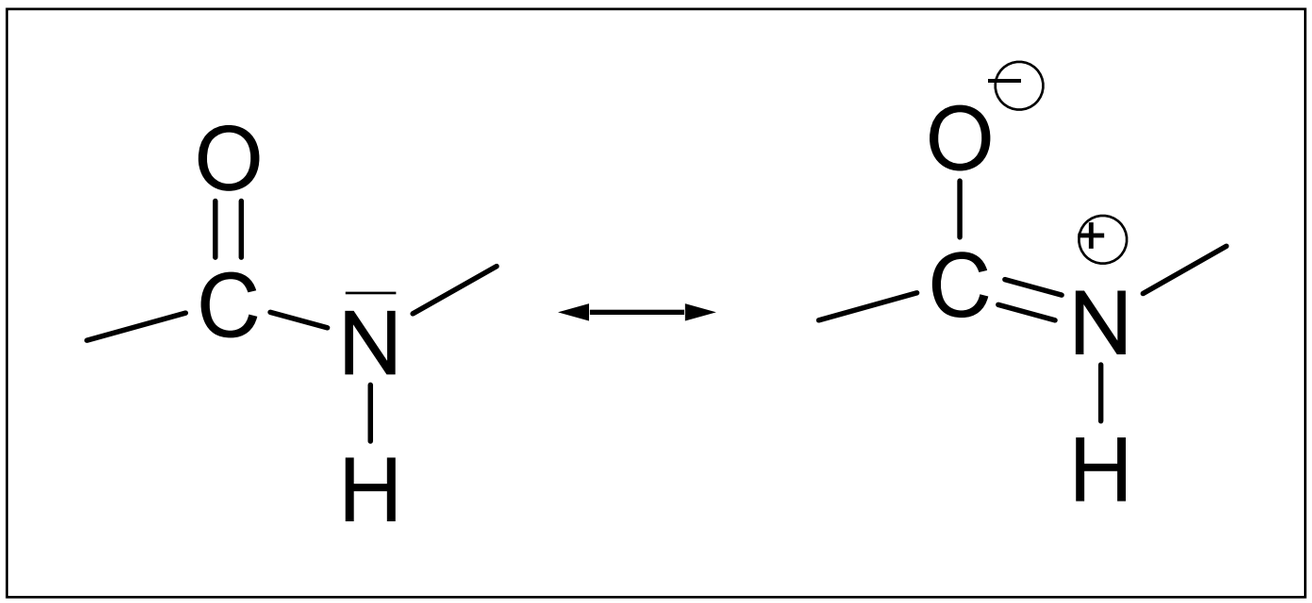
Exercise

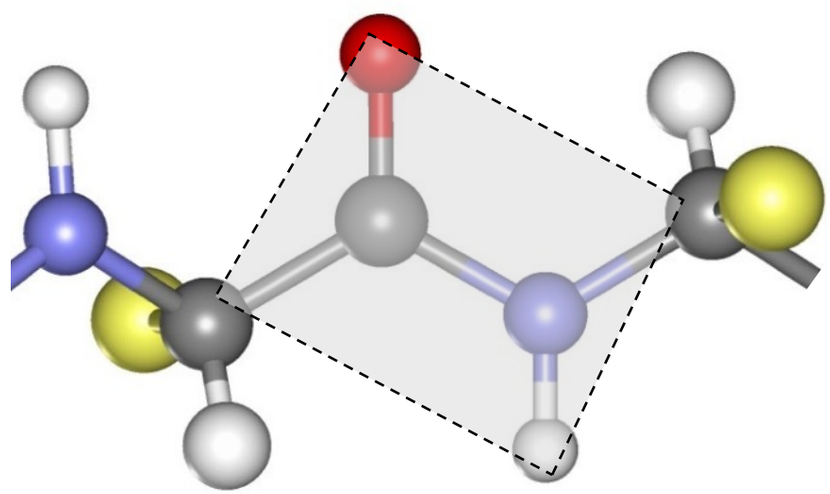
(two people)

Three peptide:

- draw a peptide from three different residues
- show rotatable bonds
- show atoms capable of forming hydrogen bonds
- discuss polarities of residue

Mesomeric structure of amide (Peptide bond)





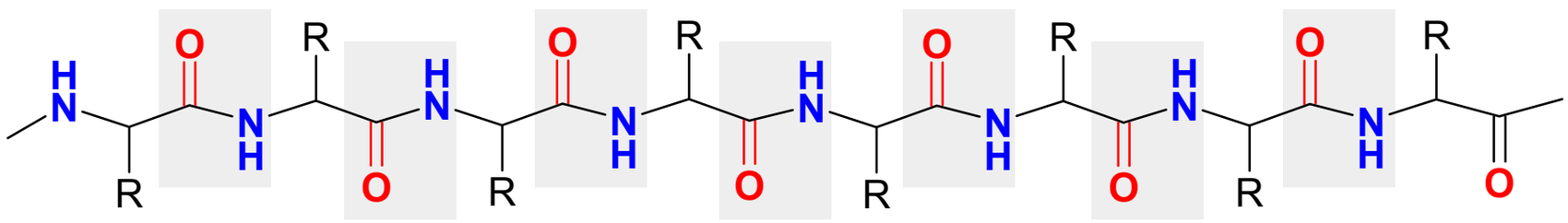
partially double bond of the C-N bond (mesomeric)

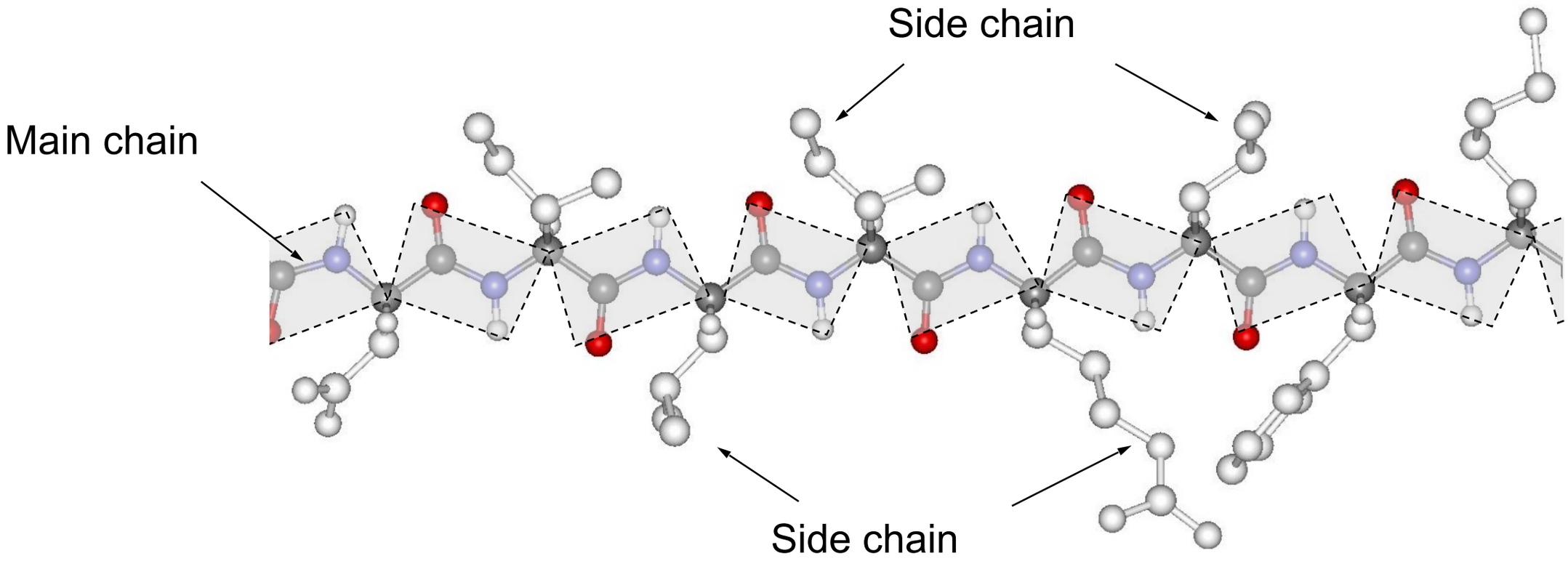
- neutral
- not rotatable

Extended structure of polypeptide chain

Peptides are rigid and not flexible here

Polypeptide





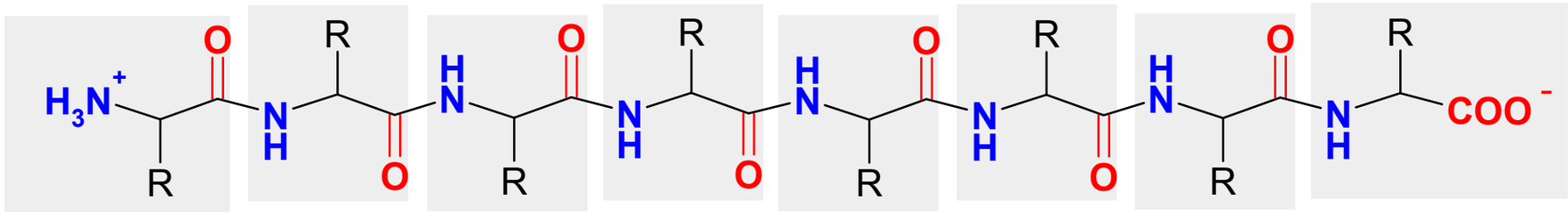
Primary structure (sequence)

Primary structure (sequence):
Sequence of amino acids in polypeptides / proteins

Amino terminus
("N-terminus")

Carboxy terminus
("C-terminus")

Peptide or protein

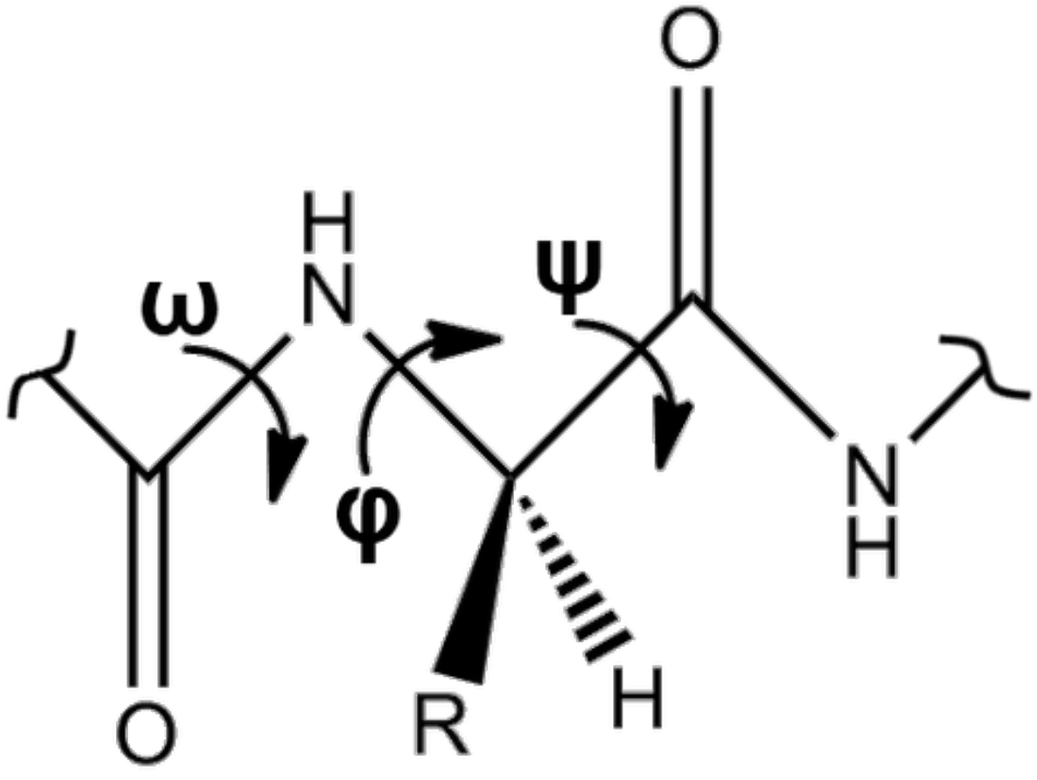


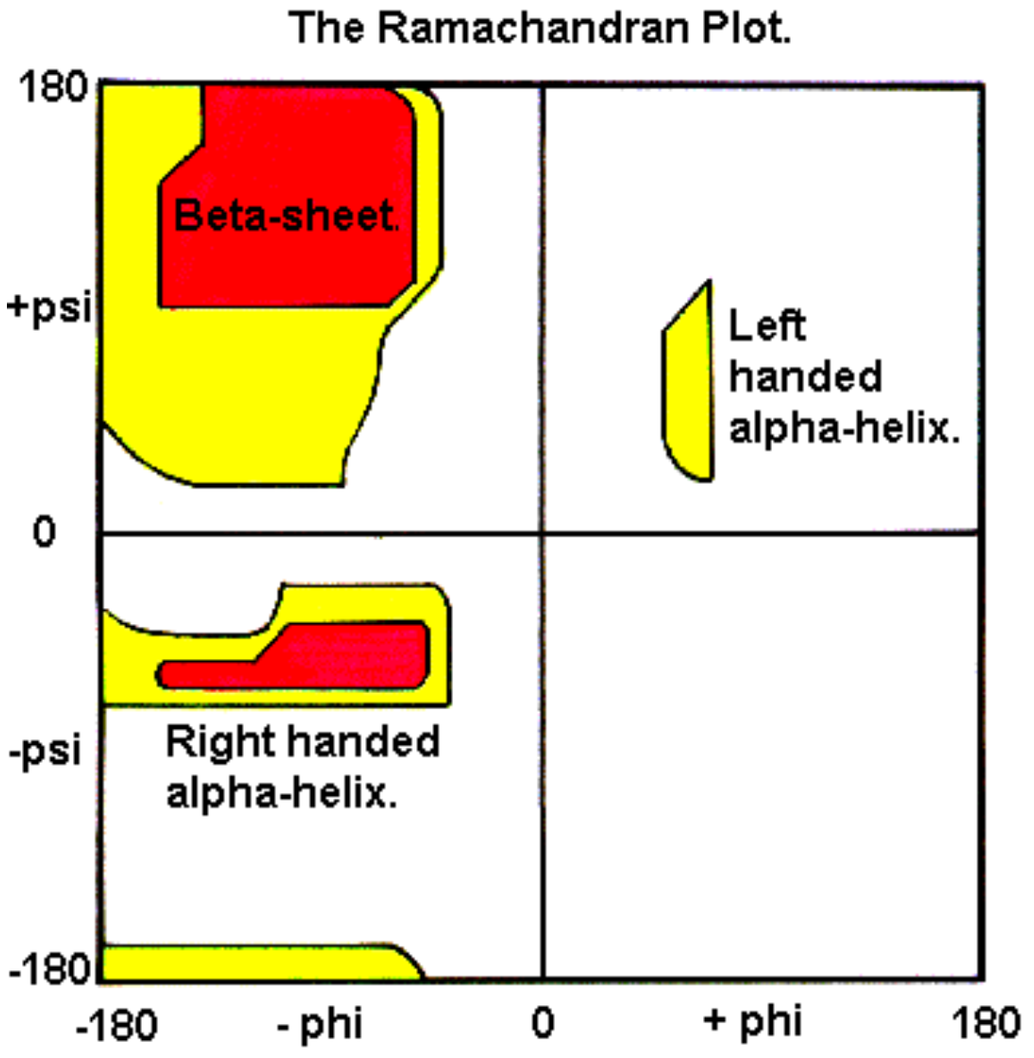
- sequence is genetically encoded
- sequence determines 3D-structure

Movie of folding

Structure of Polypeptide

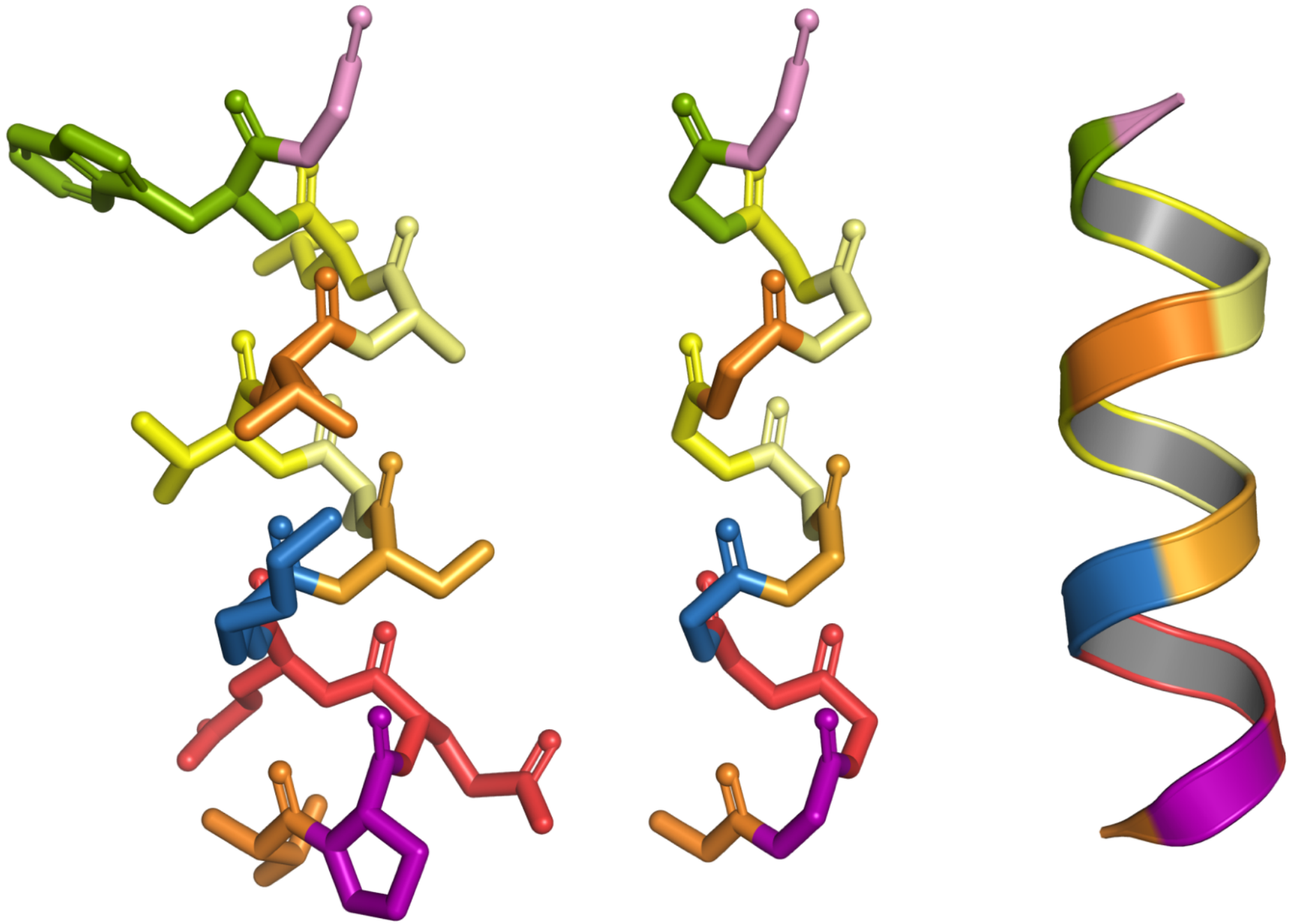
- ω = the C-N bond, not rotatable
- φ = rotatable N-C bond
- ψ = rotatable C-C bond





Protein structure

Gly
Trp
Leu
Ala
Thr
Val
Ala
Ser
Lys
Glu
Glu
Pro
Thr



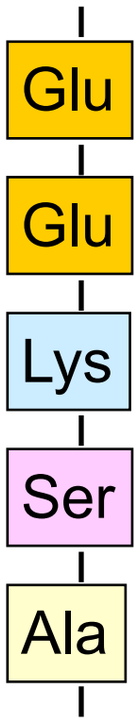
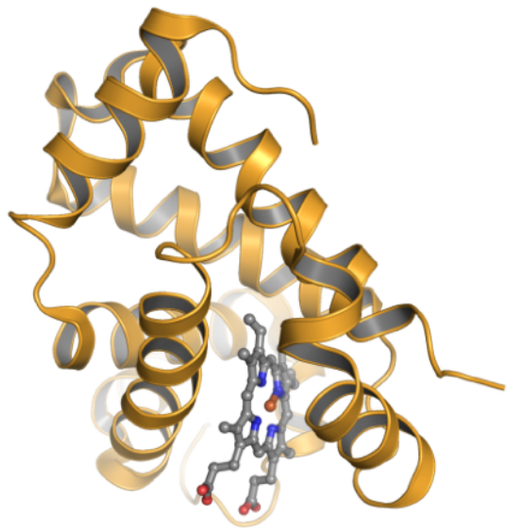
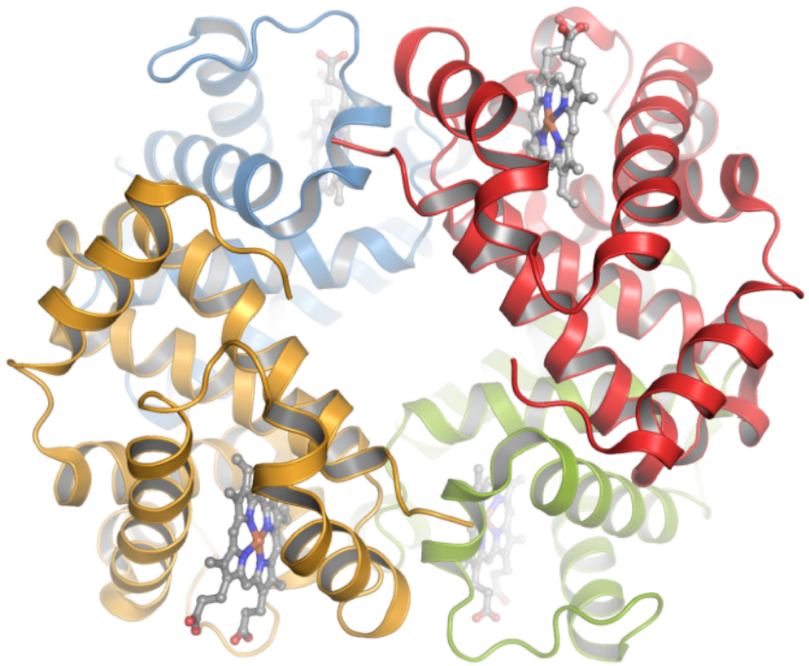
Sequence (segment)

Main and side chains ‚sticks‘

Main chain ‚backbone‘

schematic ‚Cartoon‘

Proteines: hierarchy

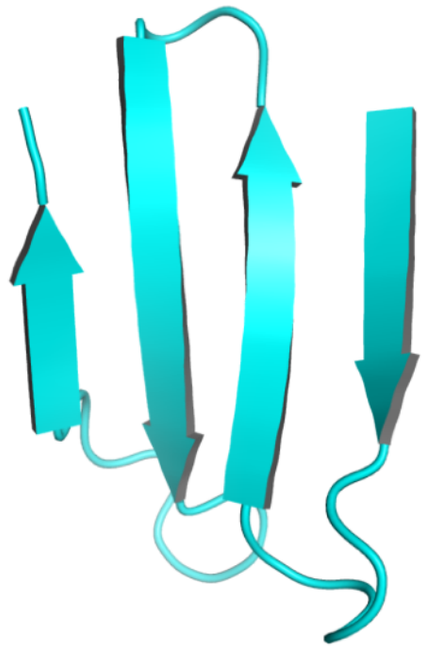
Primary structure	Secondary structure	Tertiary structure	Quaternary structure
			
covalent bonds (sequence)	Sements are folded	Chain folds to a 3D structure	Complex of several subunits

Secondary structures

Secondary structure:
Folded parts of the polypeptide chain

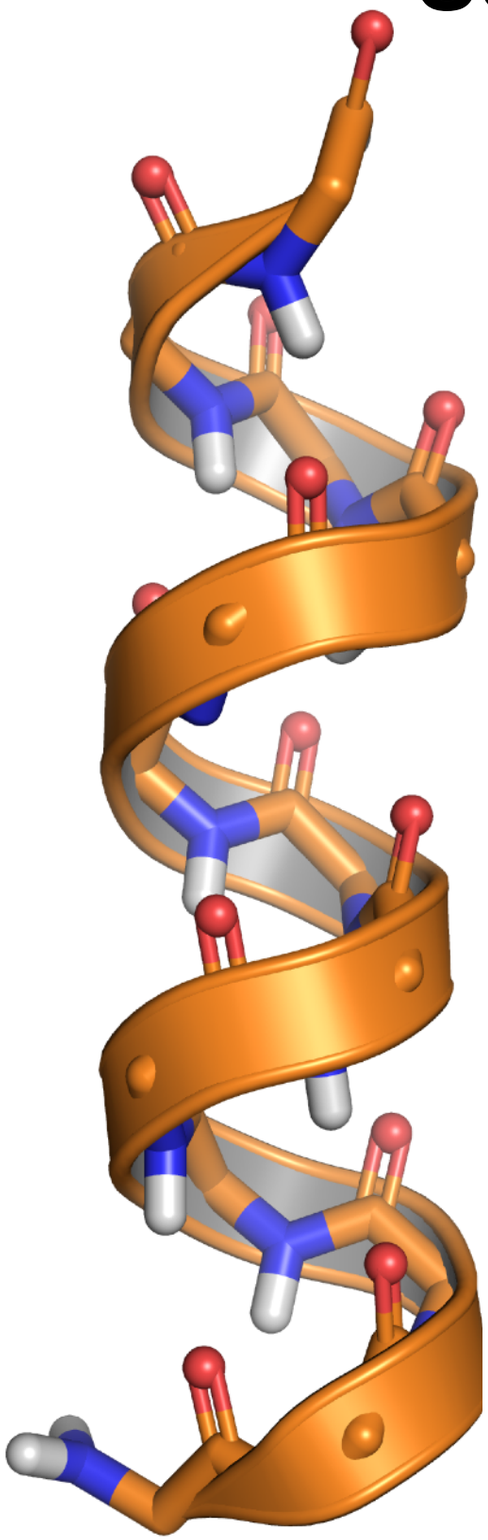
α-Helix

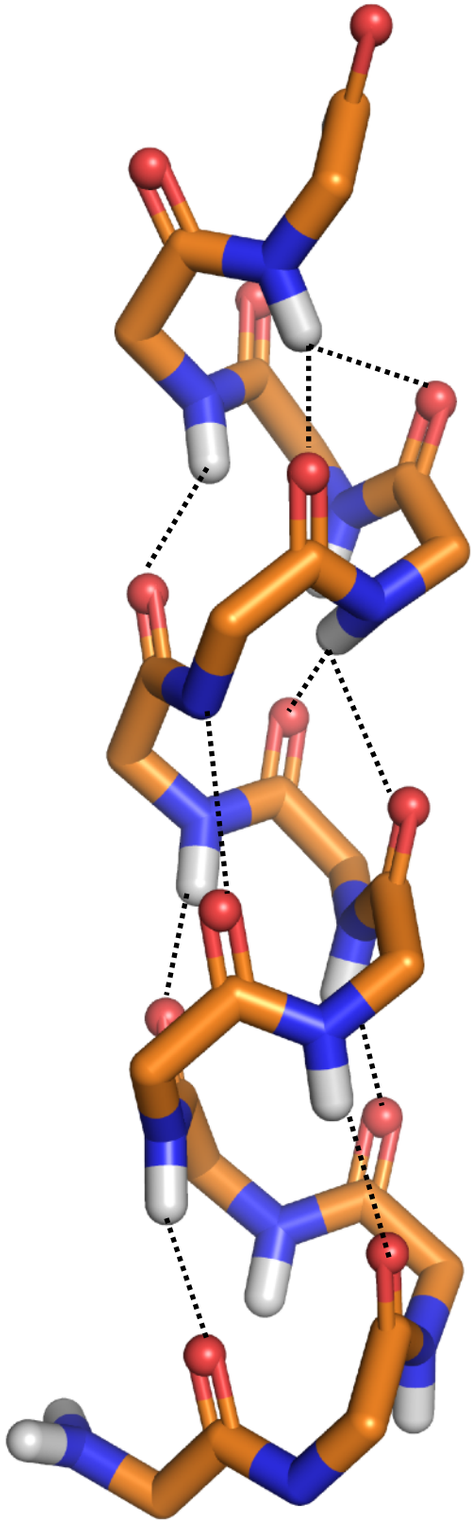
β-sheet

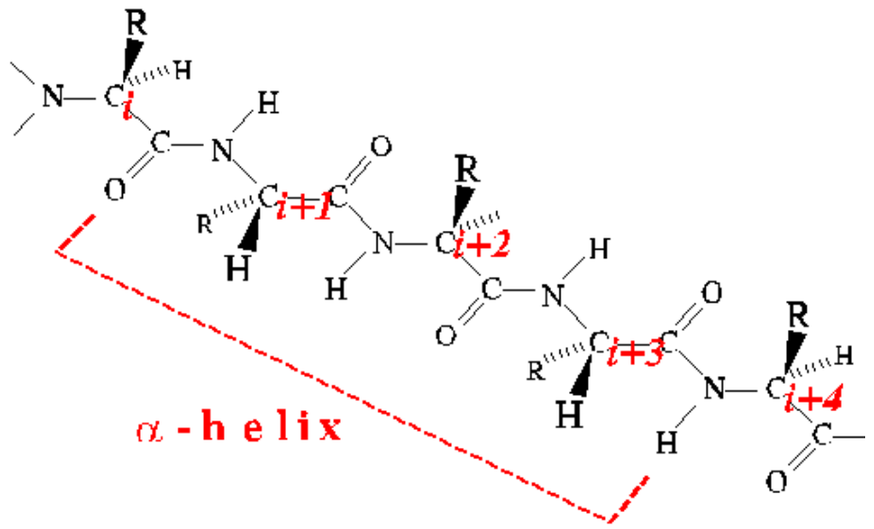


Stabilized through side chains of main chain

Secondary structure: α-helix





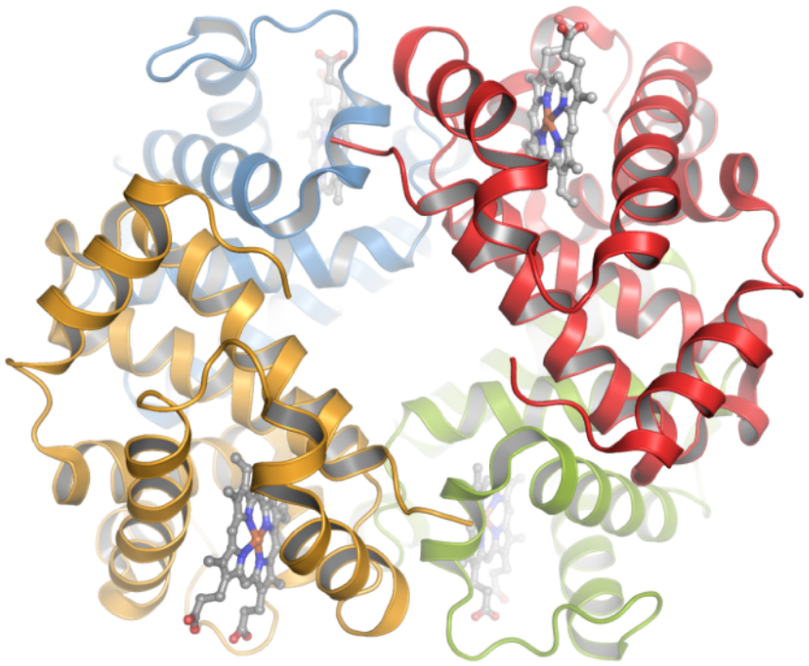


- The **C=O** of a residue (i) is hydrogen bonds to the **N-H** group of the residue (i+4)
- 3.6 residues per winding
- 1.4 Å (0,14 nm) shift / residue
- 5.4 Å pitch / winding

Secondary structure: α-Helix

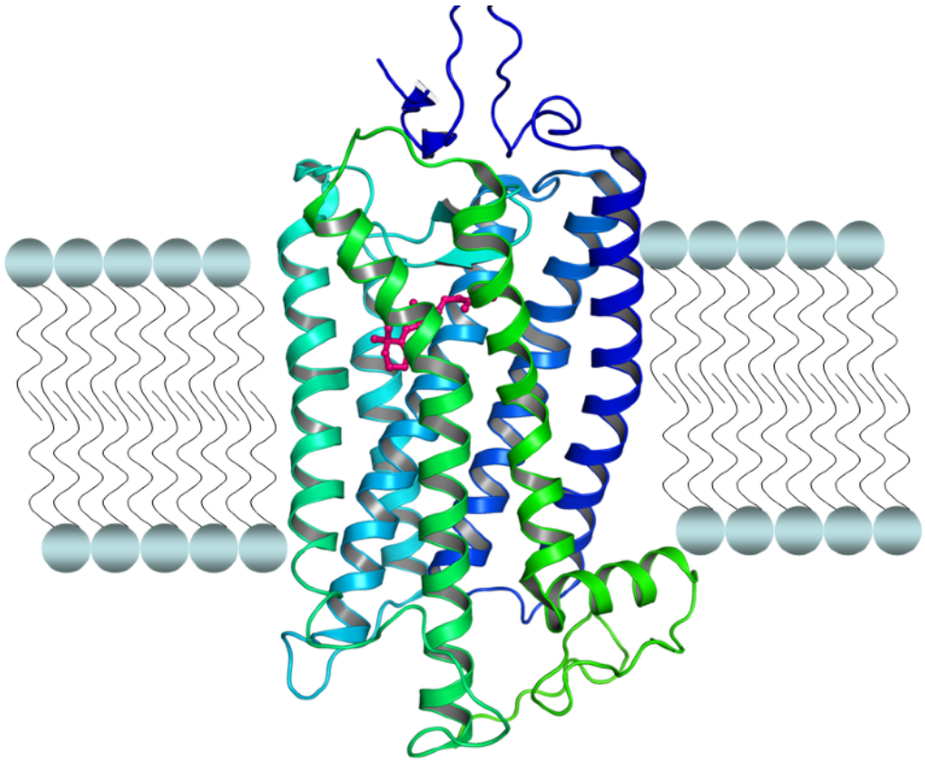
Protein with high α-content:

soluble proteins



Hämoglobin

Membrane proteins



Heptahelical
receptors
GPCR

Hepta helical receptors
G-Protein coupled Rezeptors (GPCR)

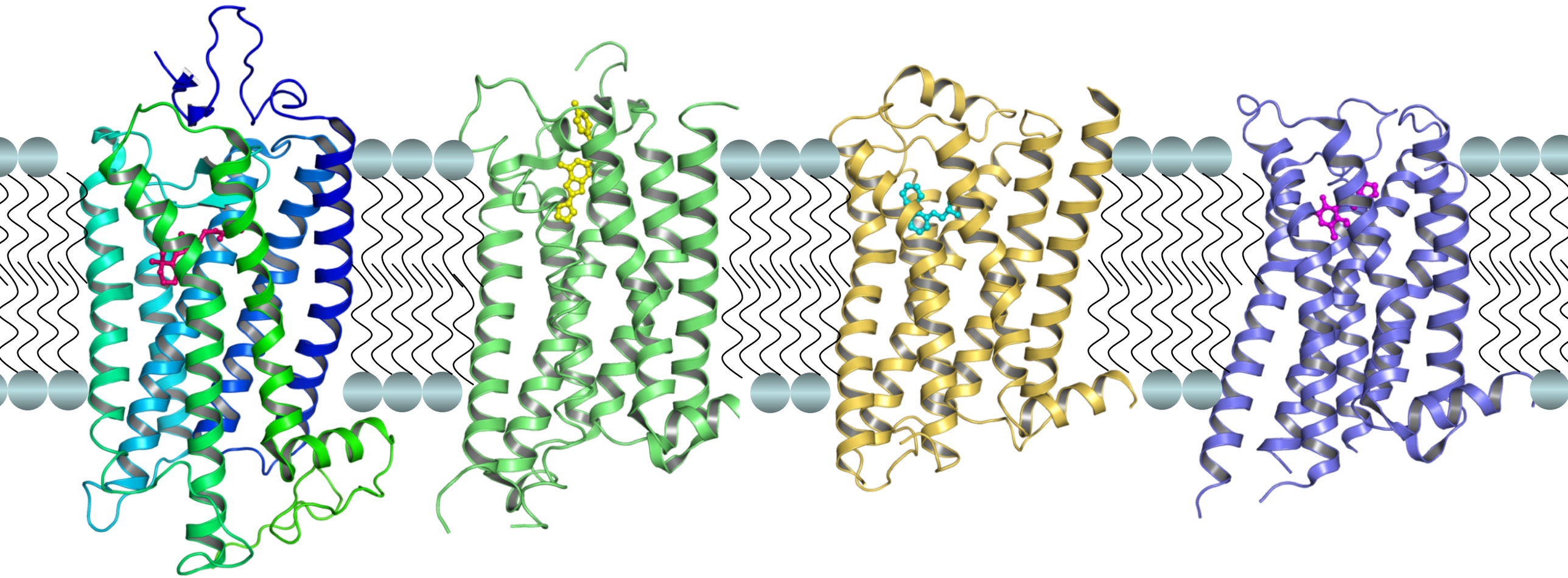
3-4 % of genes of the human genom encode > 1000 GPCRs

Licht/Retinal

Purin

Adrenalin

Dopamin



Rhodopsin

A2A

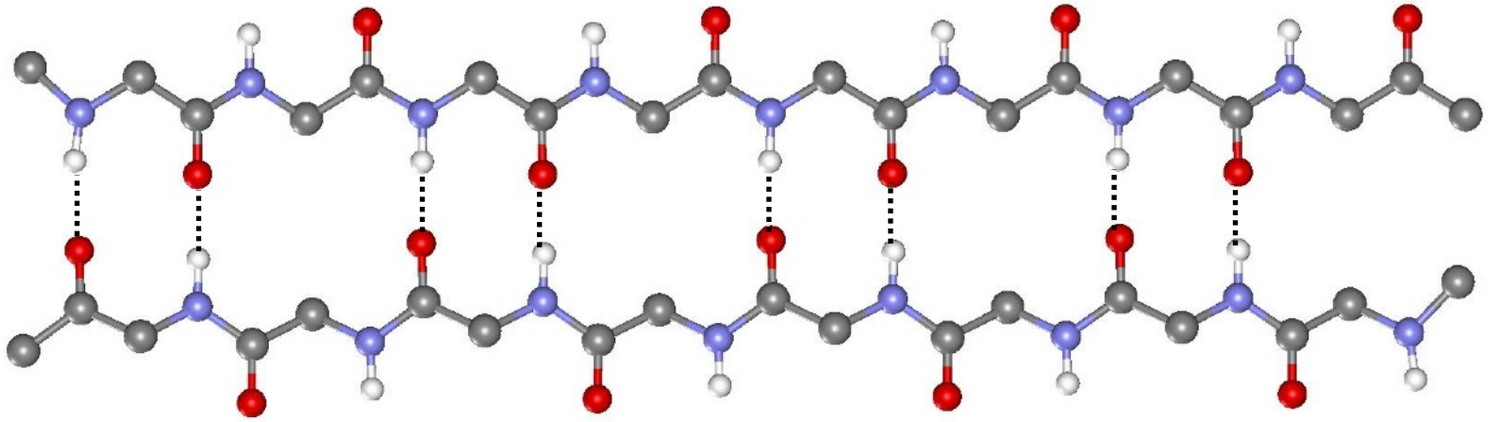
Adrenoceptor

D3

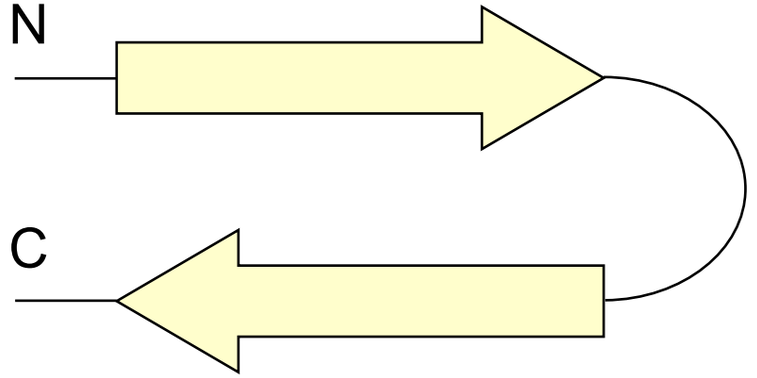
Secondary structure: β-sheet

antiparallel:

N → C

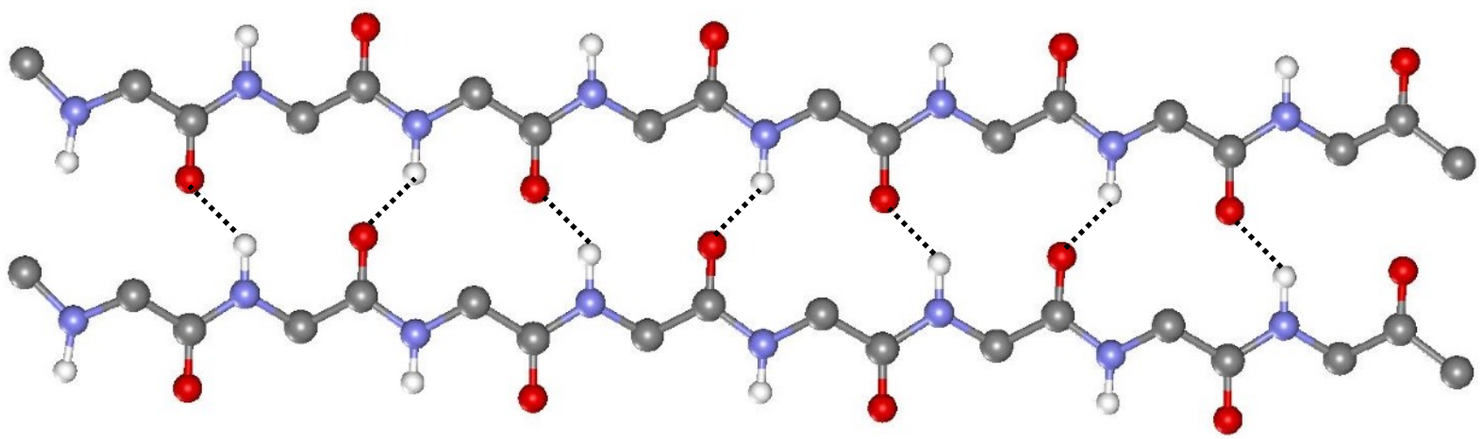


C ← N

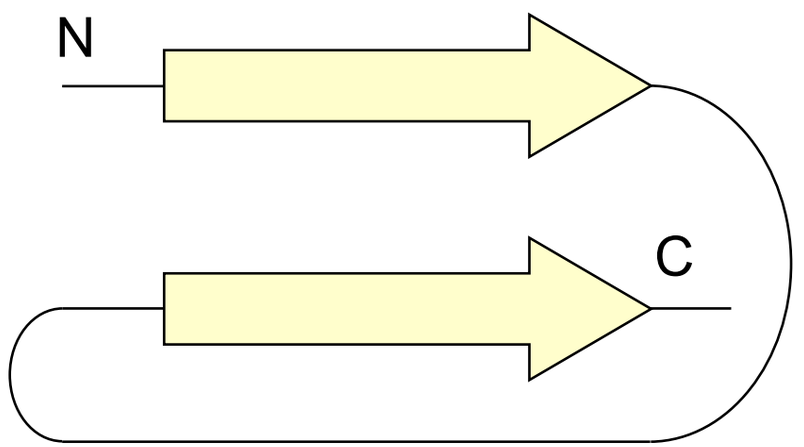


parallel:

N → C



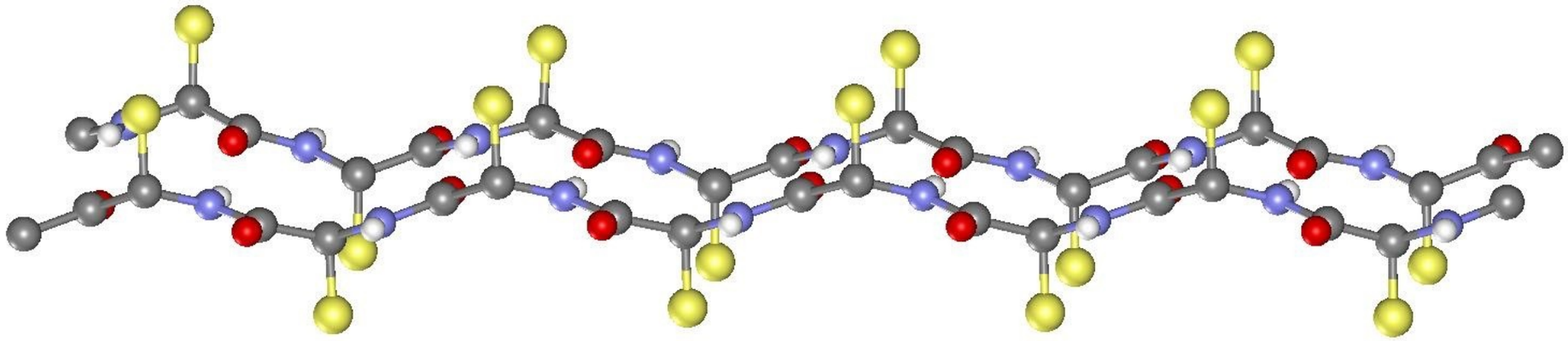
N → C



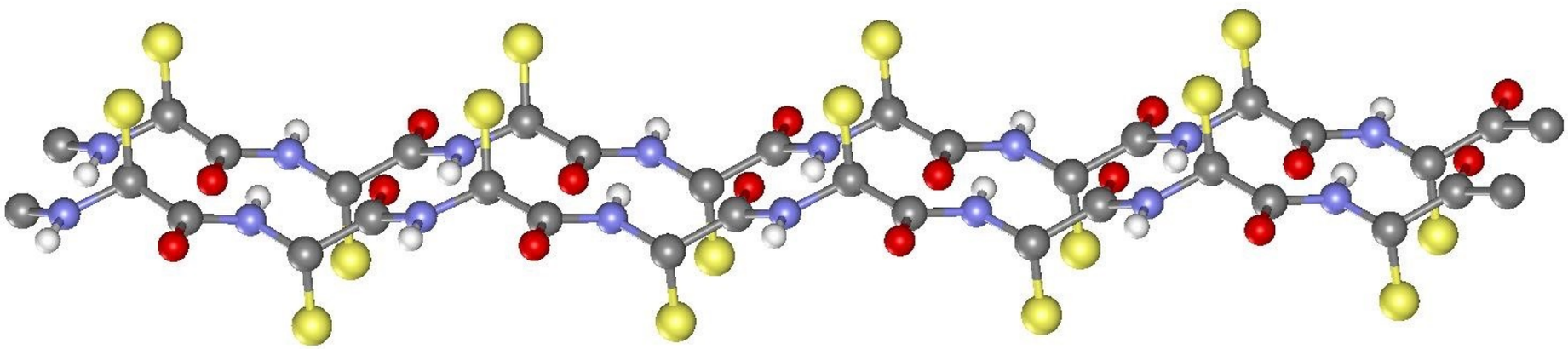
secondary structure: β-sheet

Side view

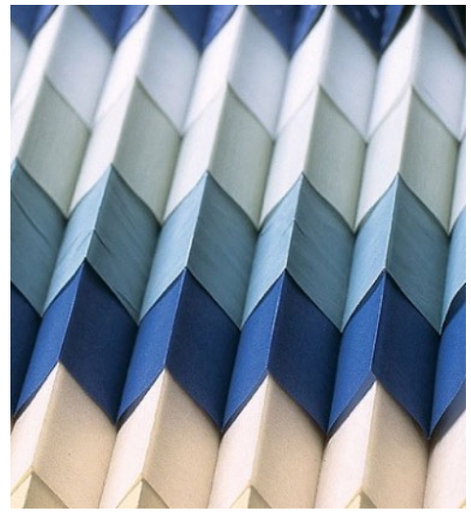
antiparallel:



parallel:



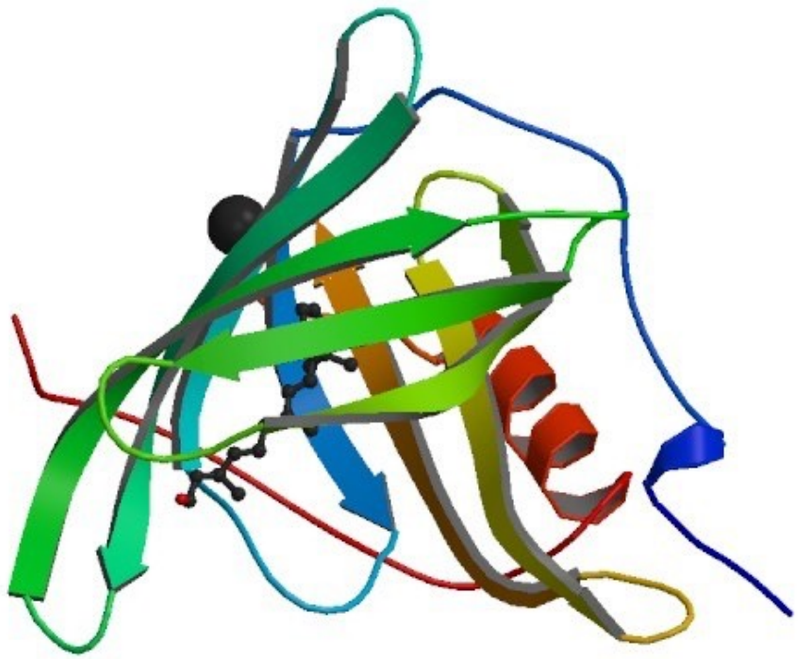
Plissee form



Secondary structure: β-sheet

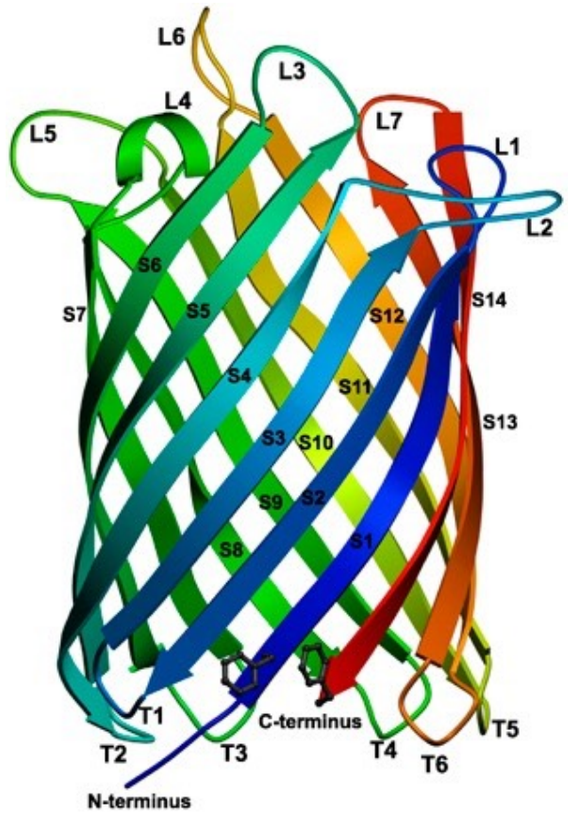
Proteins with high content of β-sheet:

soluble proteins

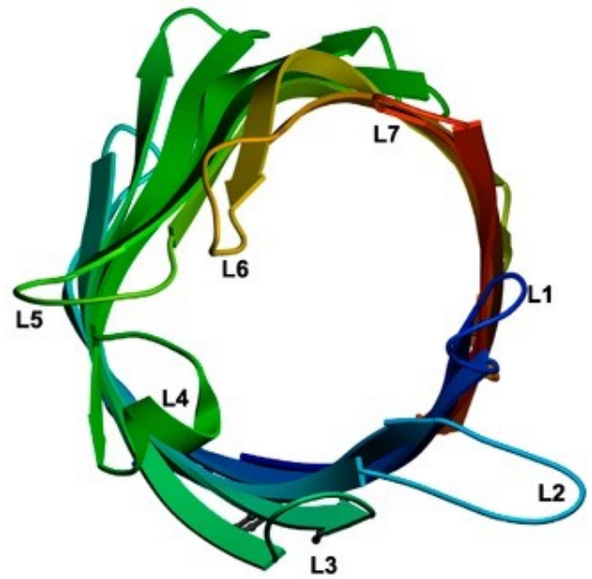


transport of retinol

Membrane proteins



side view

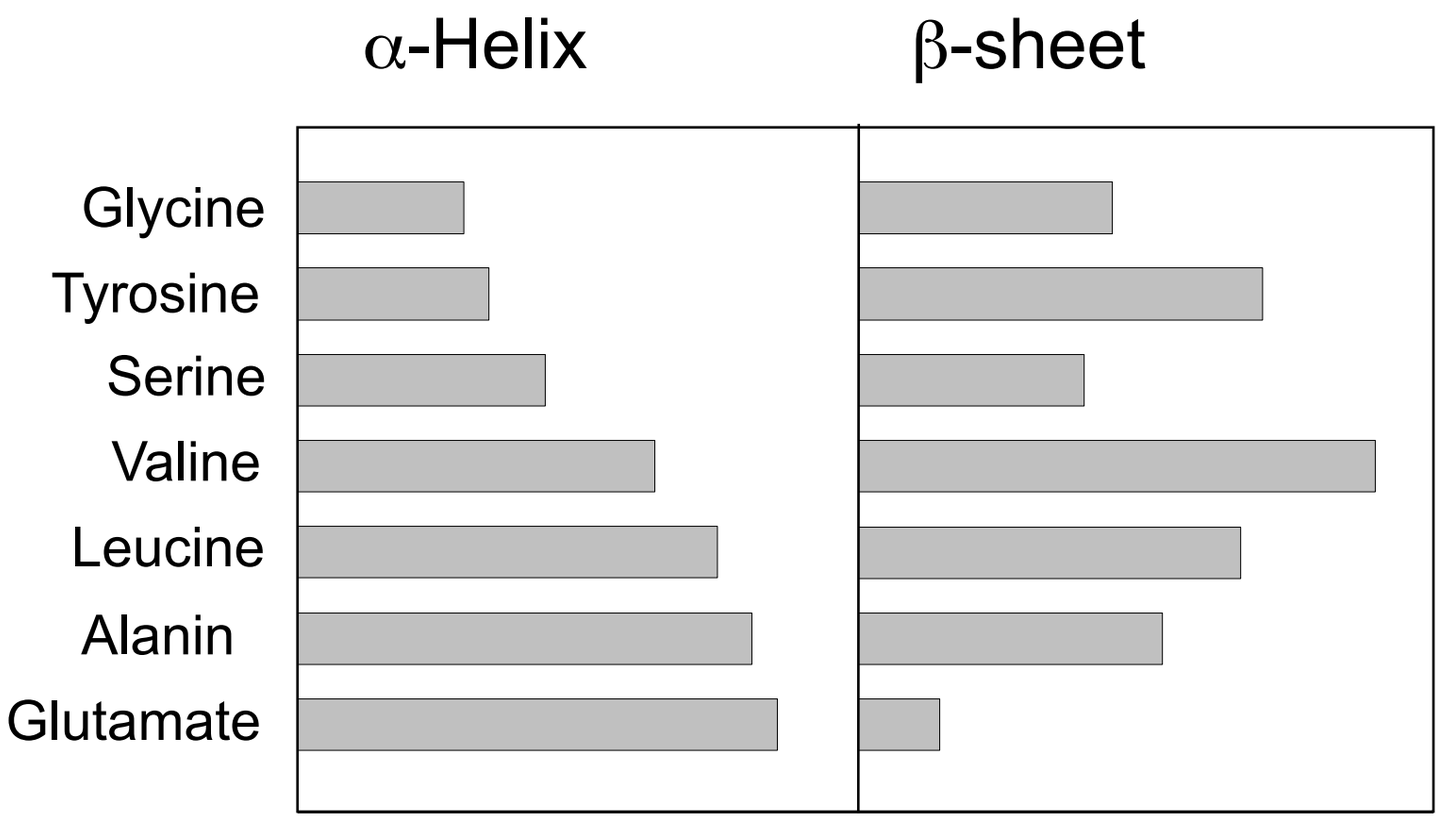


top view

pores

Secondary structure

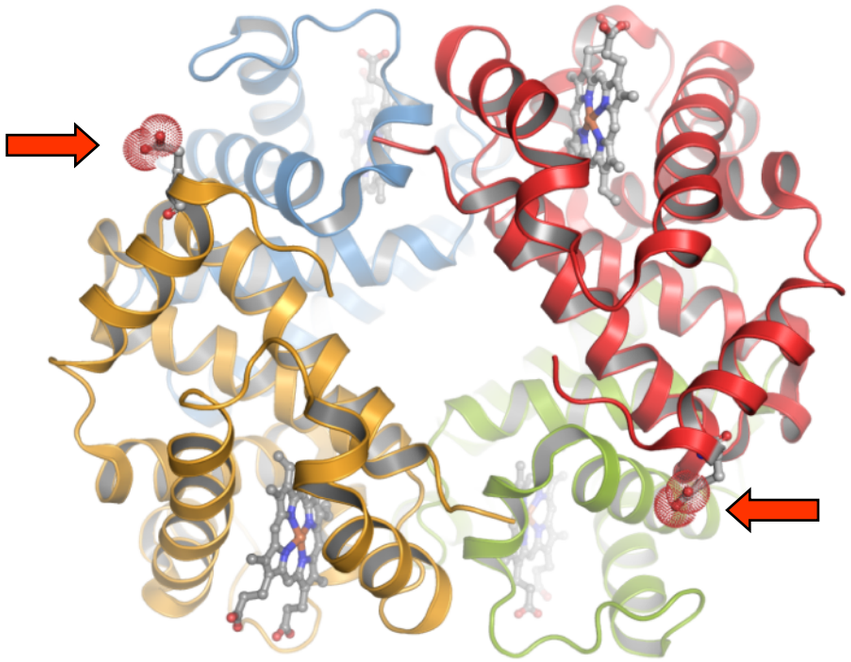
Amino acid properties
determine structure

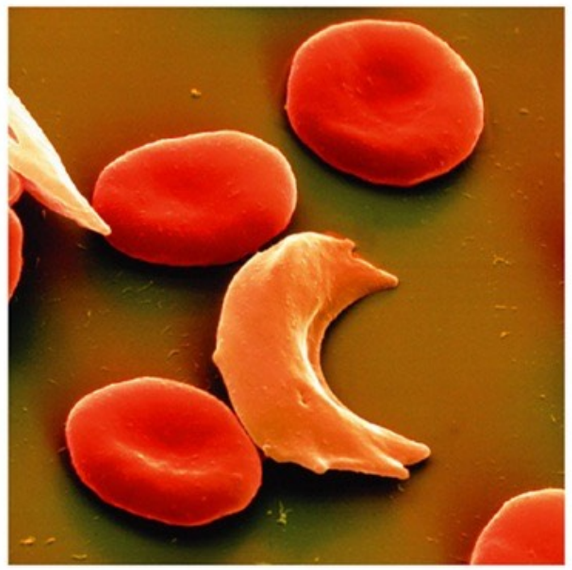


Relative propensity of an amino acid

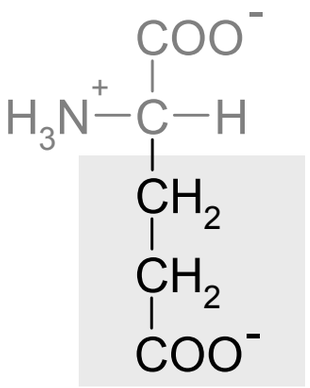
A single point mutation **can** significantly change a proteins structure / function

Amino acid determines structure and function of proteins

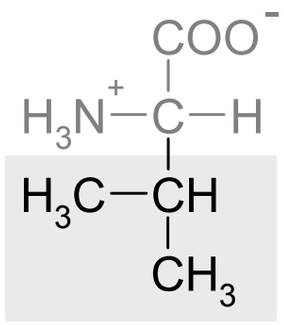




<u>Sickle cell hemoglobin</u>:
Point mutation in β-chain
(exchange of glutamate
by valine at position 6)



Glutamate
(hydrophilic)



Valine
(hydrophob)

<u>Sickle cell anemia</u>

Mutation at the protein suface affects water solubility:

Change of polarity at surface (combined with O2-deficiency) leads to aggregation of hemoglobin and deformation of the erythrocyte.

Secondary structure prediction

Find the seven transmembrane helices of rhodopsin

Aminosäuresequenz des humanen Rhodopsins, Uniprot ID: P08100 (OPSD_HUMAN)

```
        10         20         30         40         50         60
MNGTEGPNFY VPFSNATGVV RSPFEYPQYY LAEPWQFSML AAYMFLLIVL GFPINFLTLY

        70         80         90        100        110        120
VTVQHKKLRT PLNYILLNLA VADLFMVLGG FTSTLYTSLH GYFVFGPTGC NLEGFFATLG

       130        140        150        160        170        180
GEIALWSLVV LAIERYVVVC KPMSNFRFGE NHAIMGVAFT WVMALACAAP PLAGWSRYIP

       190        200        210        220        230        240
EGLQCSCGID YYTLKPEVNN ESFVIYMFVV HFTIPMIIIF FCYGQLVFTV KEAAAQQQES

       250        260        270        280        290        300
ATTQKAEKEV TRMVIIMVIA FLICWVPYAS VAFYIFTHQG SNFGPIFMTI PAFFAKSAAI

       310        320        330        340
YNPVIYIMMN KQFRNCMLTT ICCGKNPLGD DEASATVSKT ETSQVAPA
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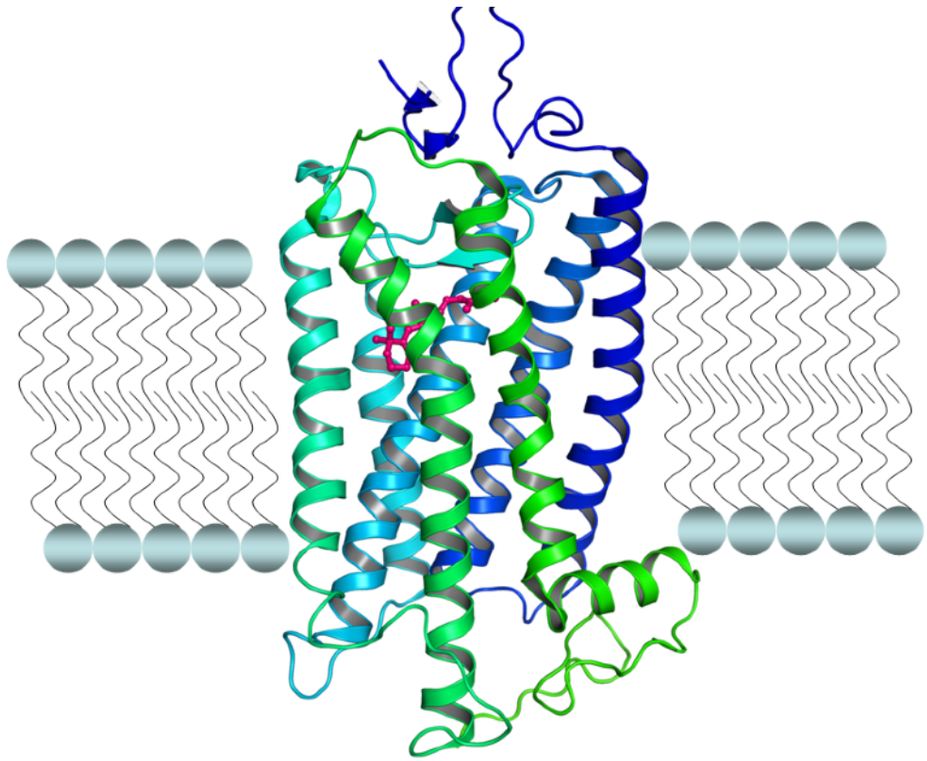
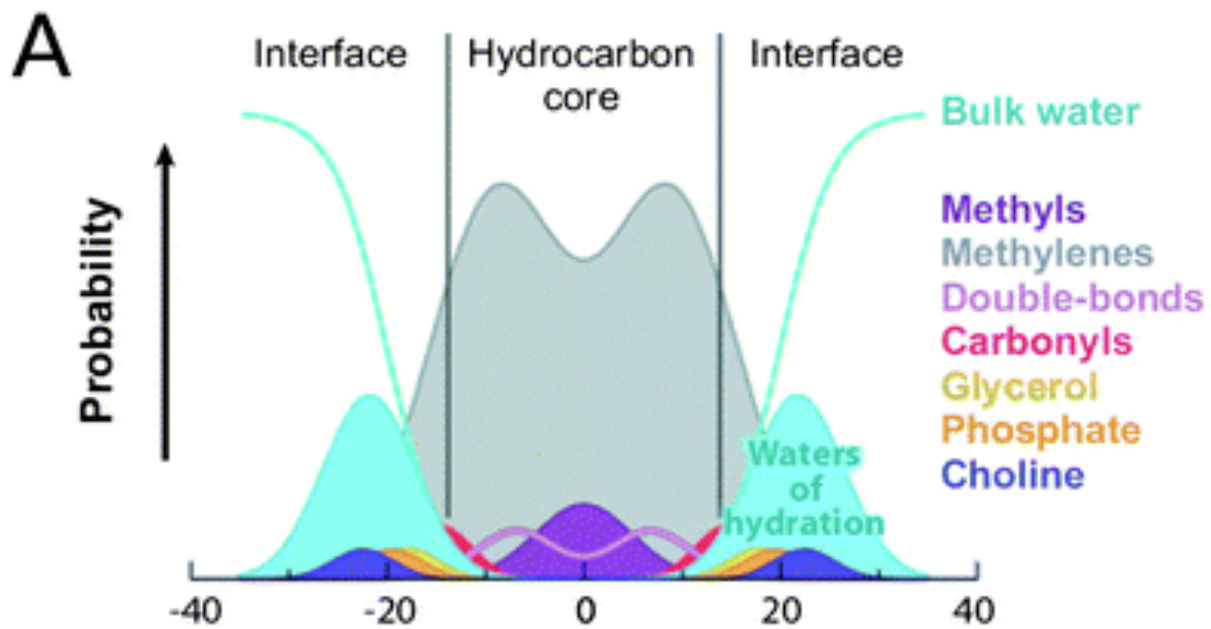
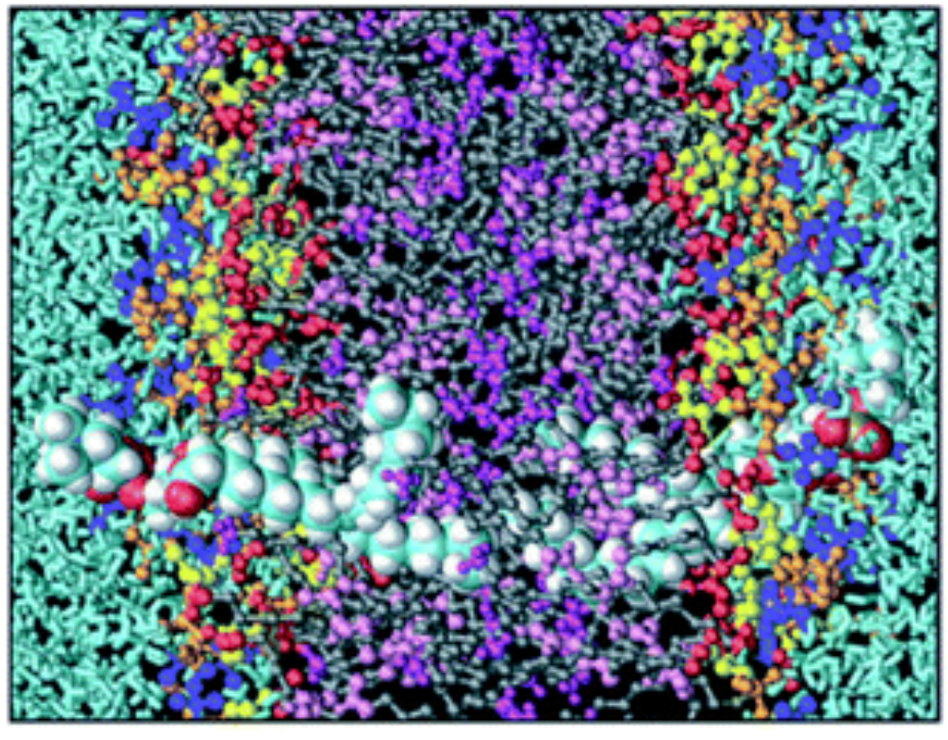


Hydrophobicity

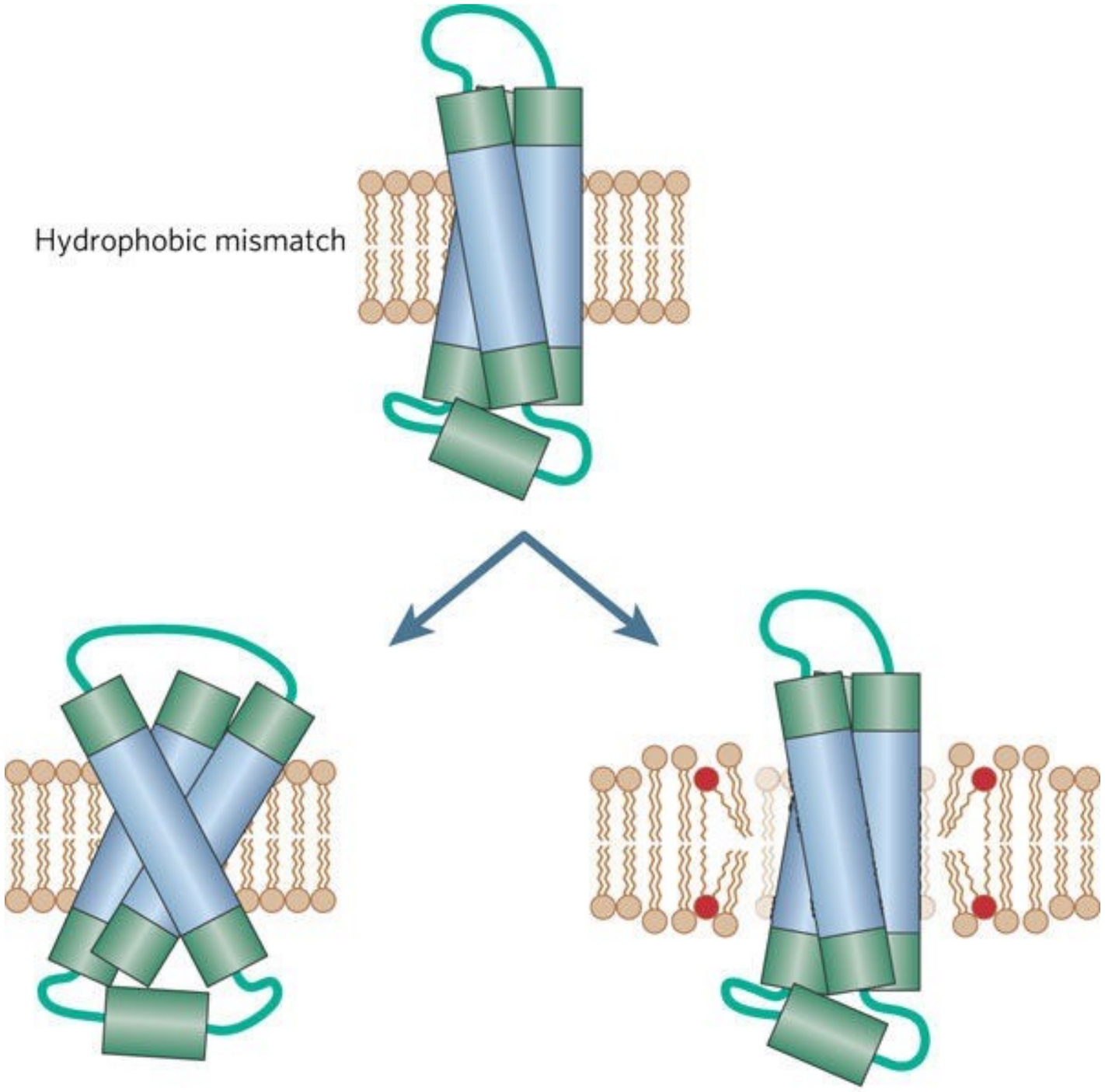
A



B

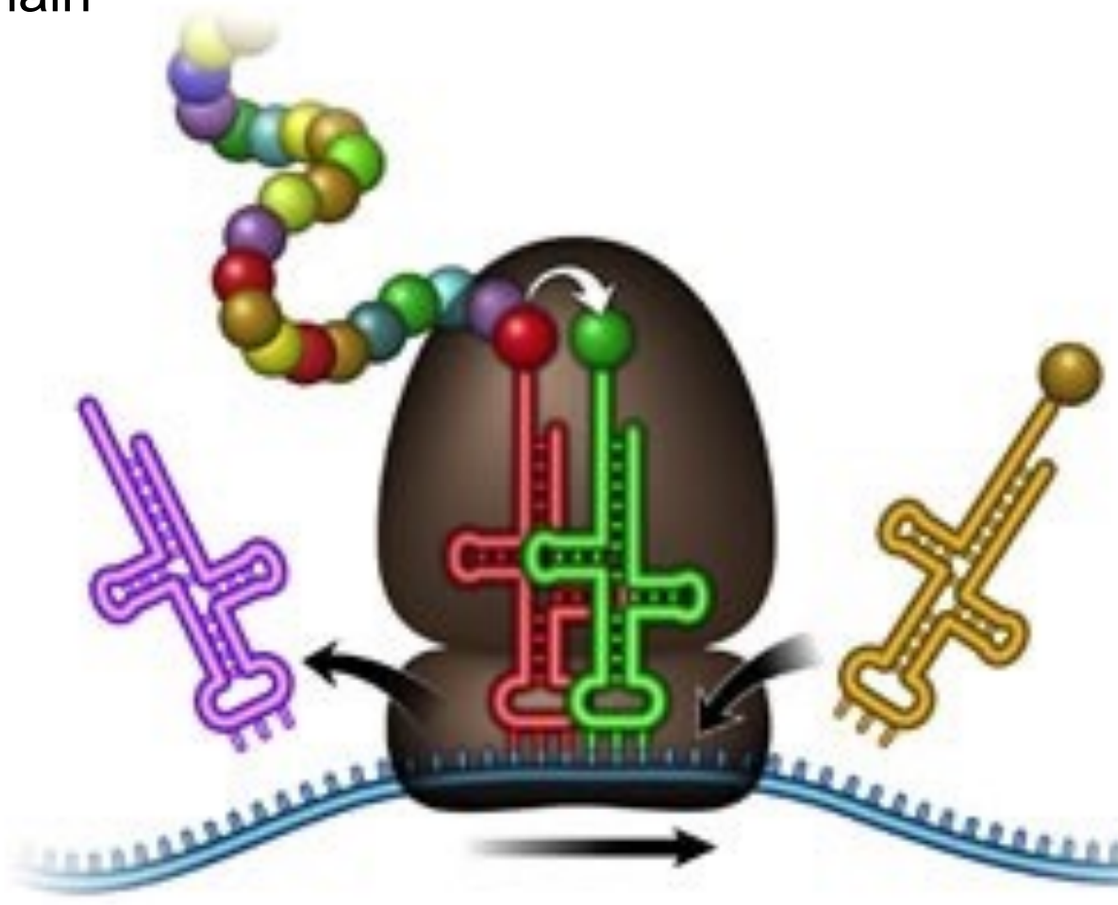


Hydrophobicity: hydrophobic mismatch

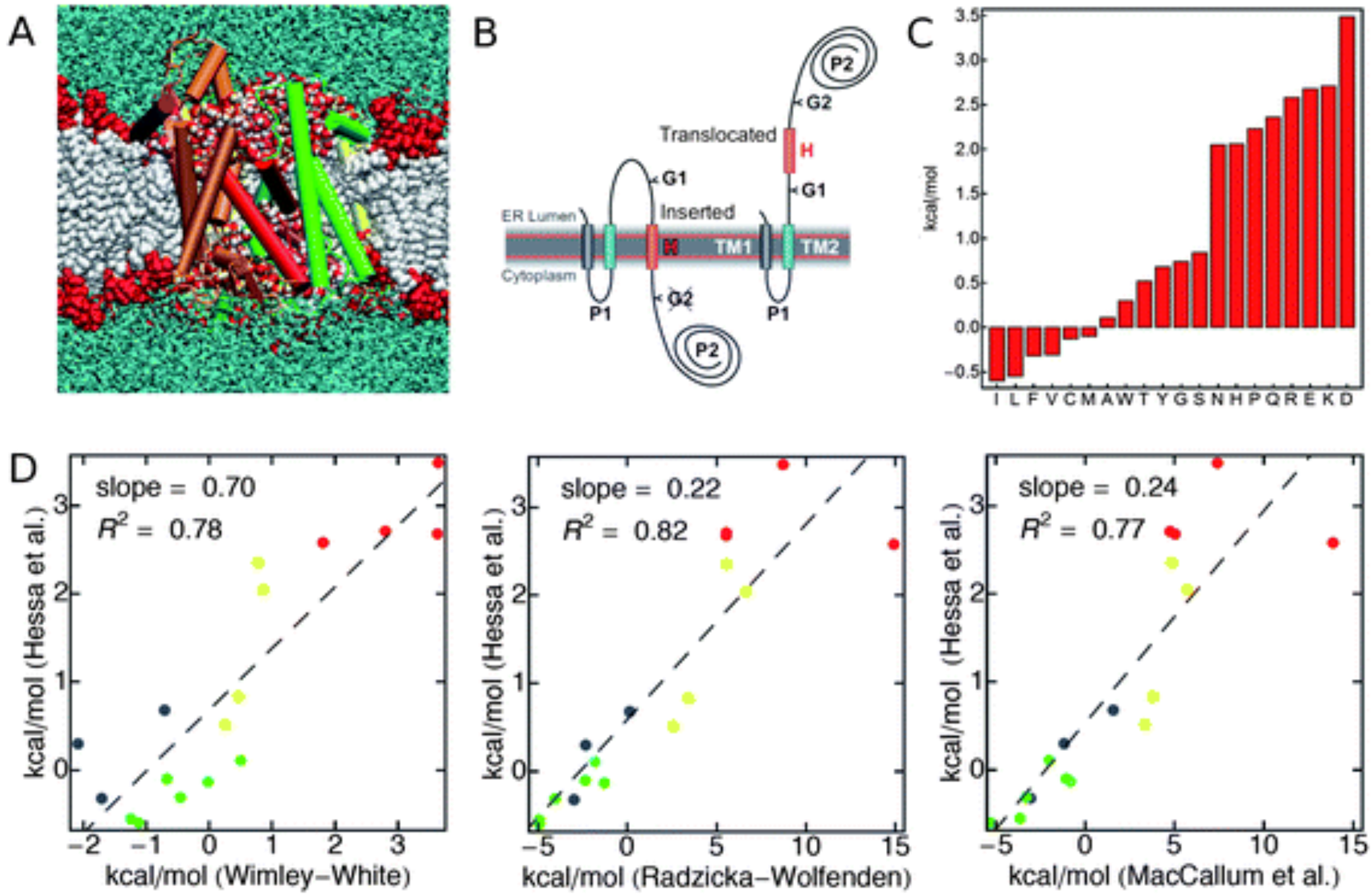


Translation

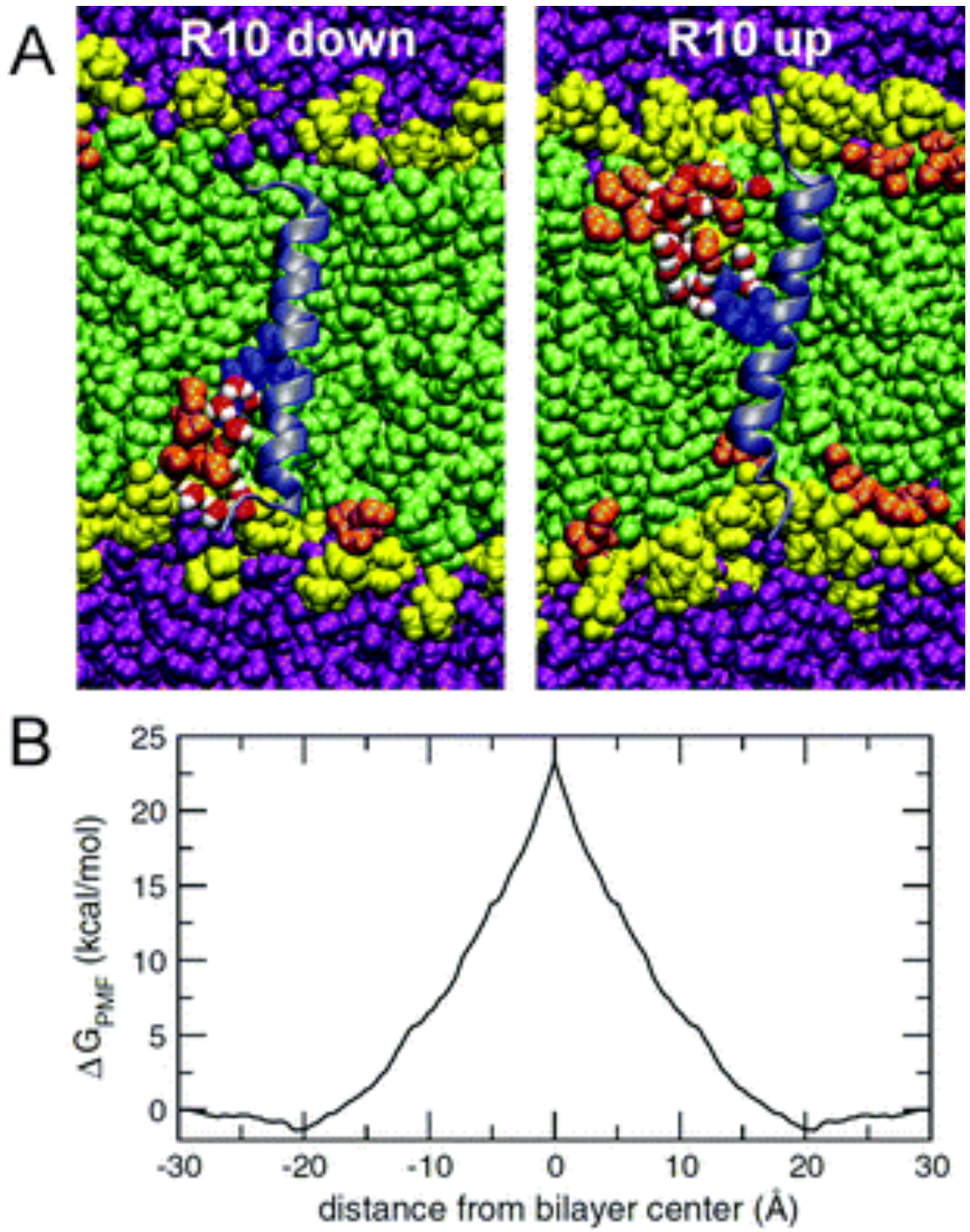
Biosynthesis of proteins at the Ribosome



Hydrophobicity and Translation

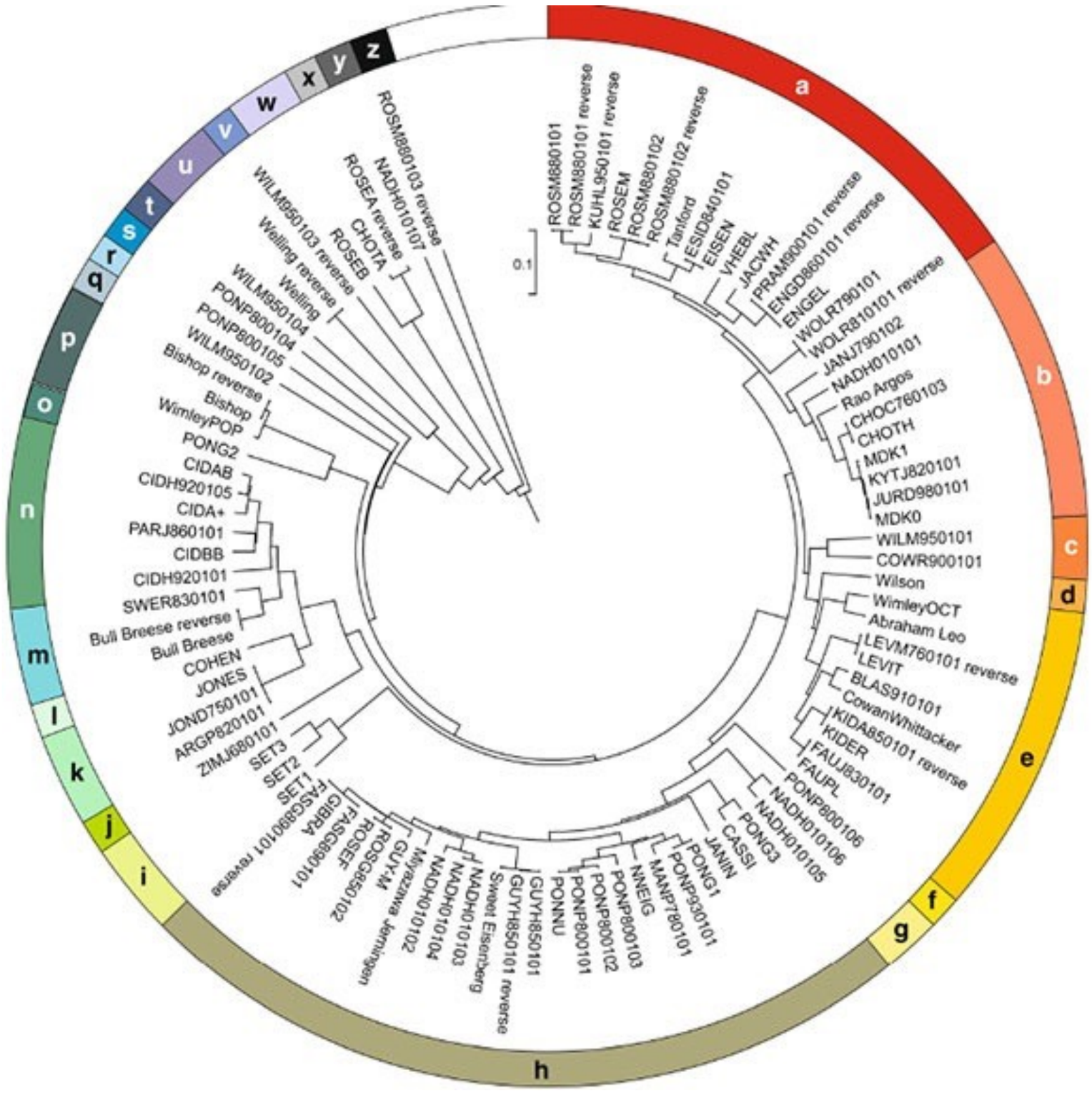


Hydrophobicity: MD simulations



Insertion of Arg

High variety of different hydrophobicity scales



Hydrophobicity plot

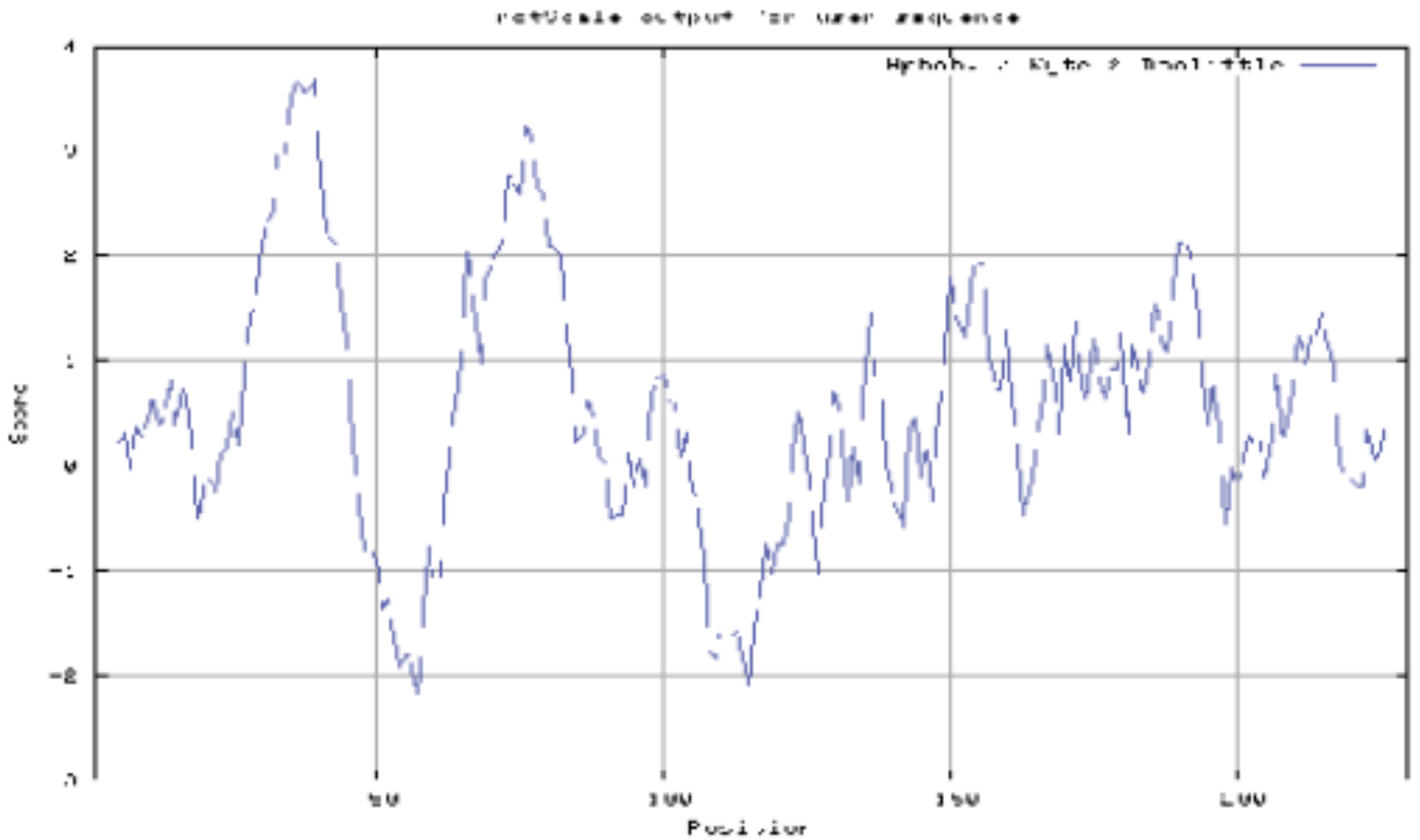
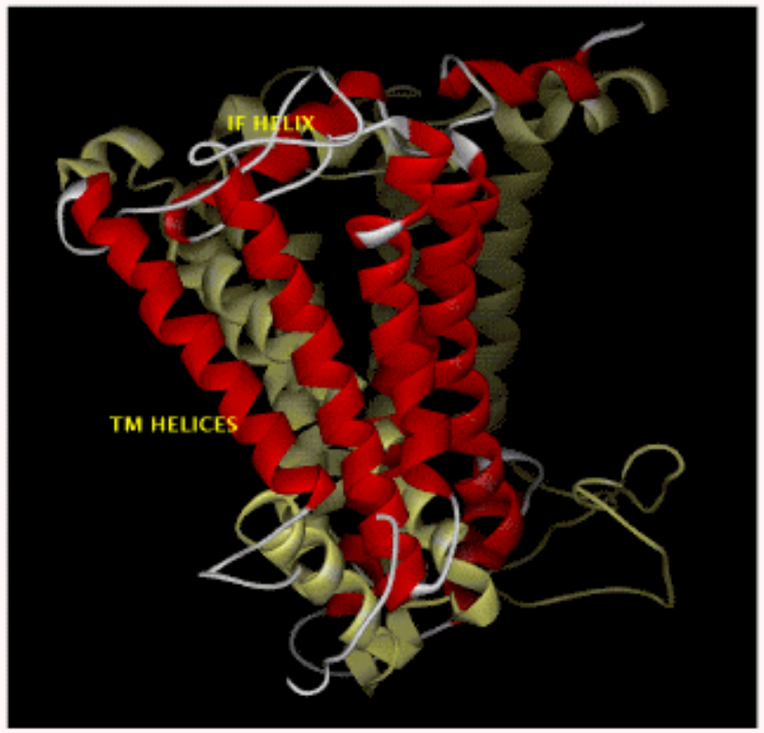
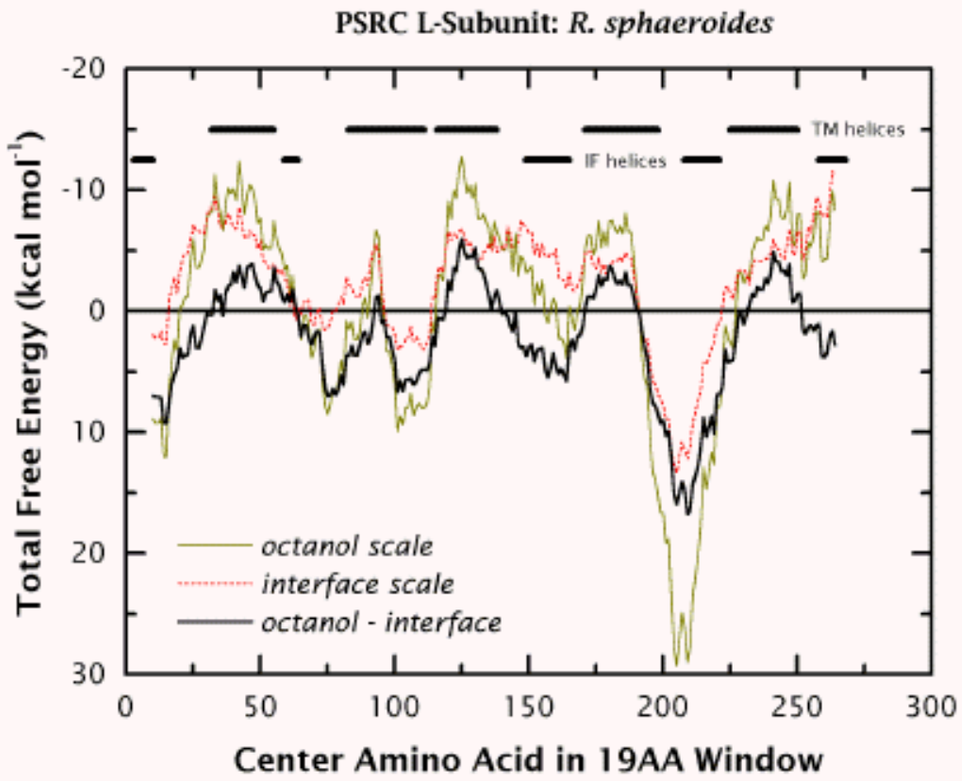


Figure 10: Kyte and Doolittle hydrophobicity plot of cytochrome c oxidase subunit II.

Hydrophobicity can be used to predict hydrophobic segments

Hydrophobicity plot





Hydrophobicity plots

https://web.expasy.org/protscale/

Secondary structure / topology prediction

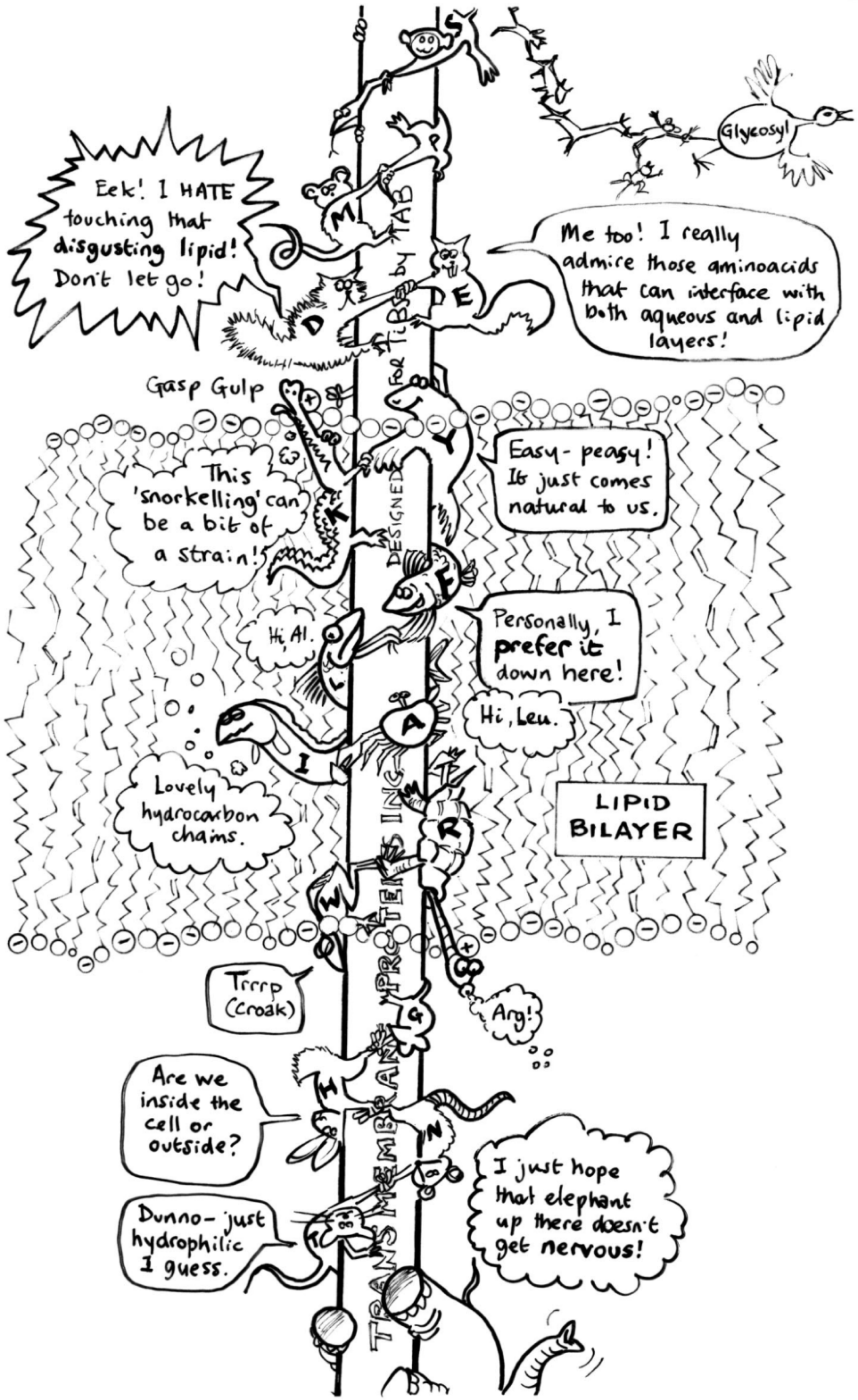
- DAS-TMfilter
- HMMTOP
- MARCOIL
- PHOBIUS
- PREDICTPROTEIN
- SOSUI
- TMHMM
- TMpred
- TopPred
- UniProt/Swiss-Prot
- Rhythm

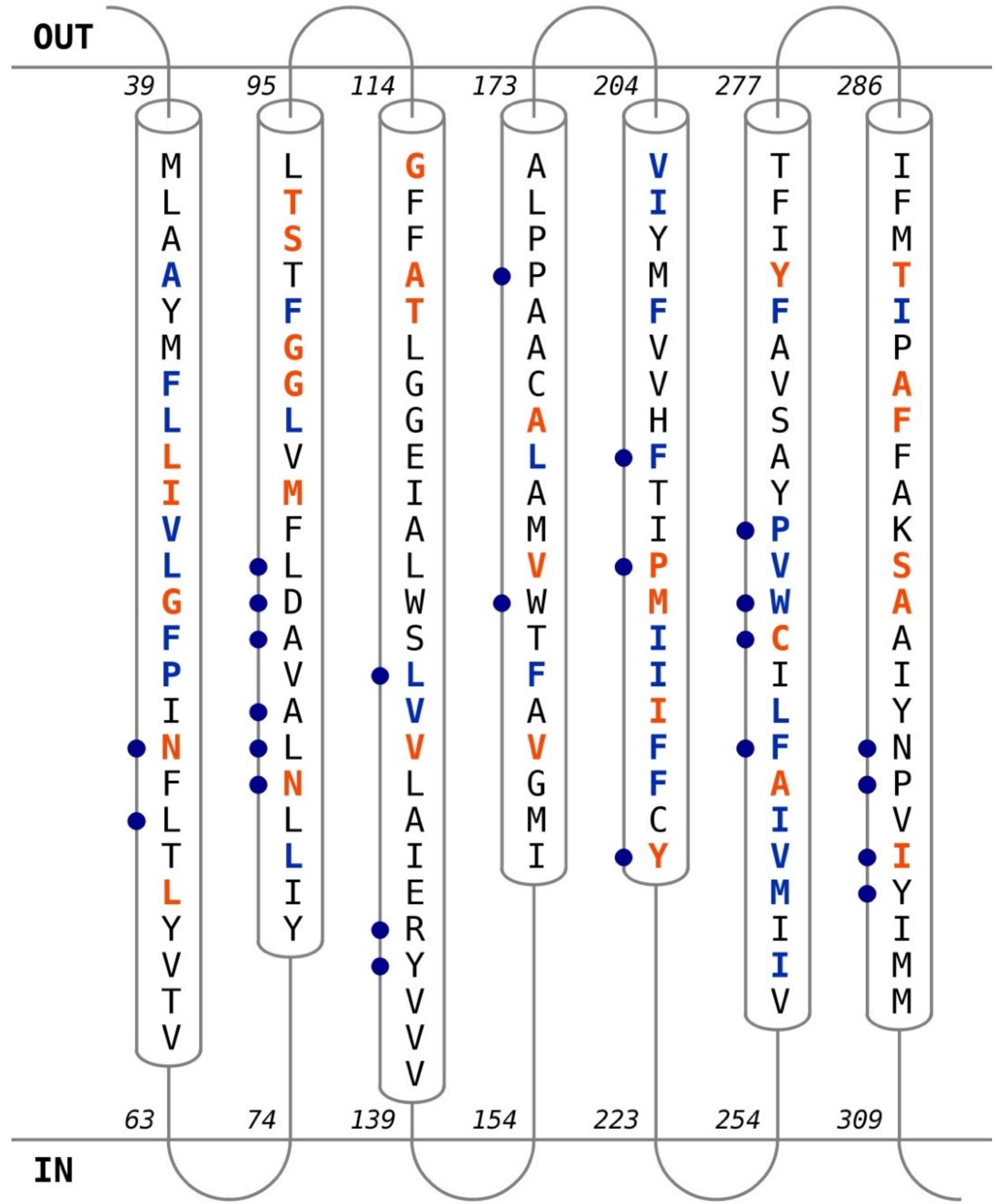
based on:

- solvent accessibility
- secondary structure
- signal peptides
- positive inside rule
- hydrophobicity

Algorithms:

- Markov Modeling
- Neuronal Networks
- Machine Learning


Eek! I HATE touching that disgusting lipid! Don't let go!
Me too! I really admire those aminoacids that can interface with both aqueous and lipid layers!
Glycosyl
DESIGNED for TiBS by TAB
Gasp Gulp
This 'snorkelling' can be a bit of a strain!
Easy-peasy! It just comes natural to us.
Hi, Al.
Personally, I prefer it down here!
Hi, Leu.
Lovely hydrocarbon chains.
LIPID BILAYER
TRANSMEMBRANE PROTEINS
Trrrp (Croak)
Arg!
Are we inside the cell or outside?
I just hope that elephant up there doesn't get nervous!
Dunno- just hydrophilic I guess.


OUT
IN
39 M L A A Y M F L L I V L G F P I N F L T L Y V T V 63
95 L T S T F G G L V M F L D A V A L N L L I Y 74
114 G F F A T L G G E I A L W S L V V L A I E R Y V V V 139
173 A L P P A A C A L A M V W T F A V G M I 154
204 V I Y M F V V H F T I P M I I I F F C Y 223
277 T F I Y F A V S A Y P V W C I L F A I V M I I V 254
286 I F M T I P A F F A K S A A I Y N P V I Y I M M 309