Protein Physics 2016

Lecture 1, January 19

Course Introduction & Simple Interactions

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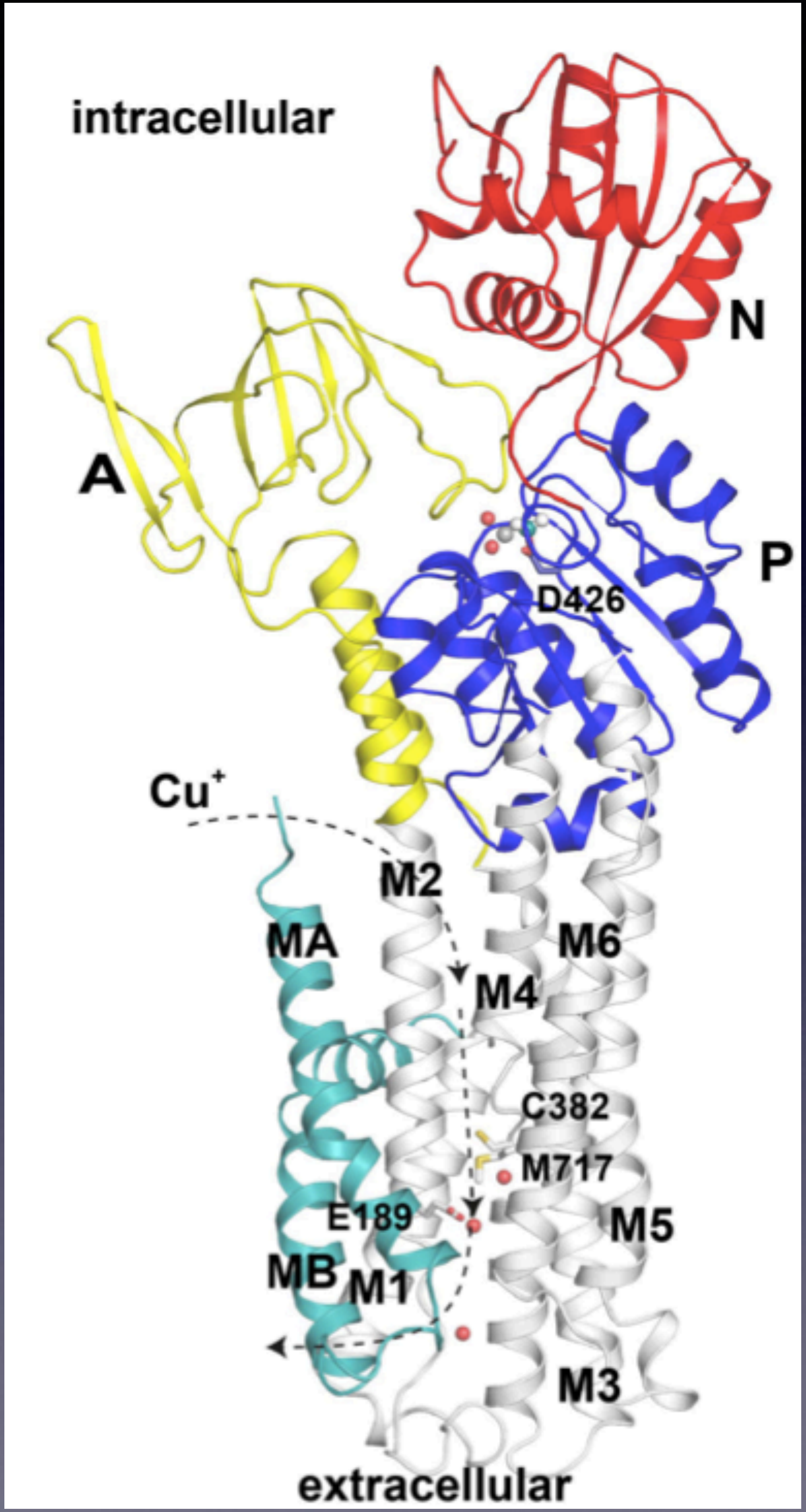
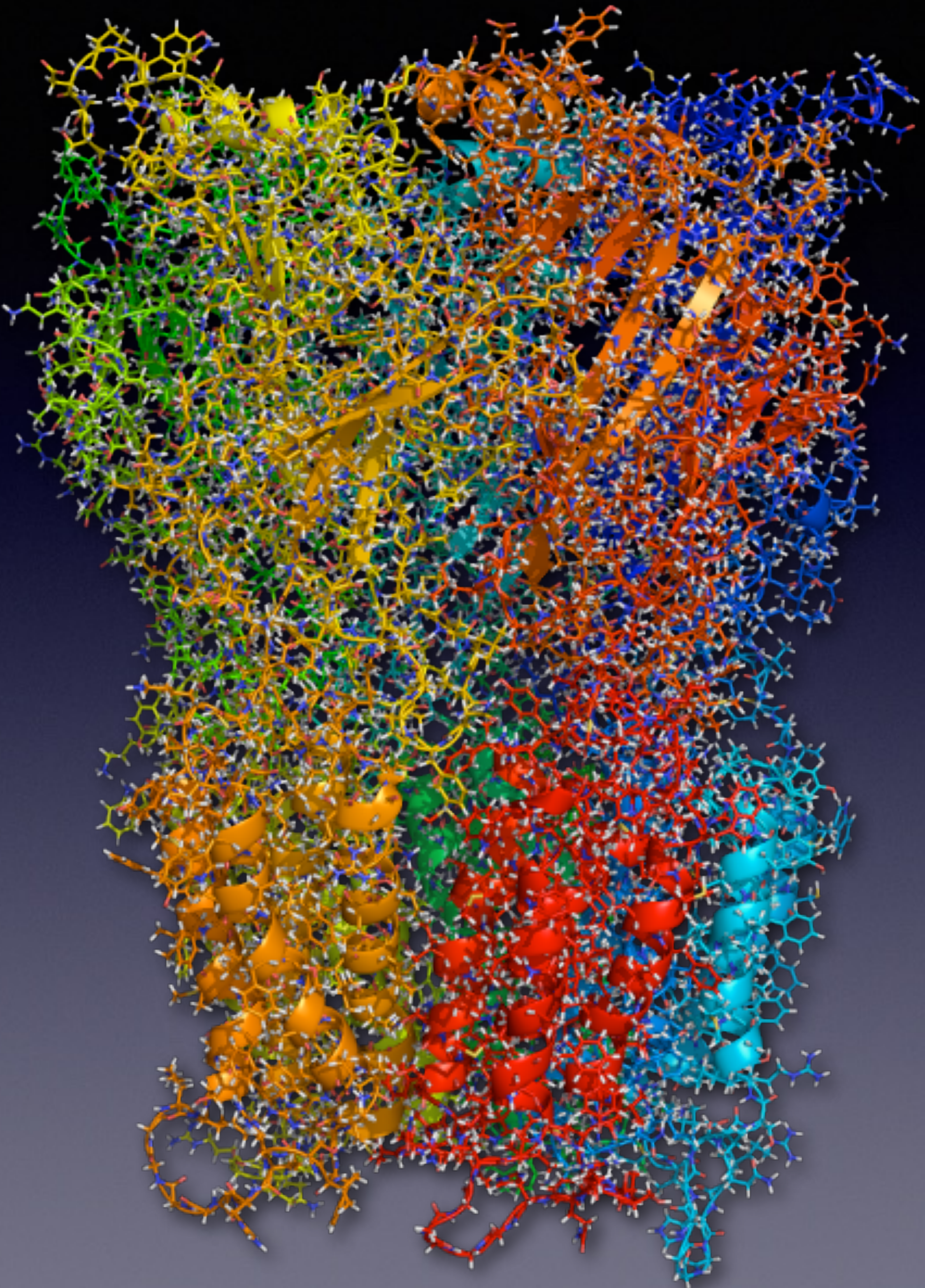
Theoretical & Computational Biophysics

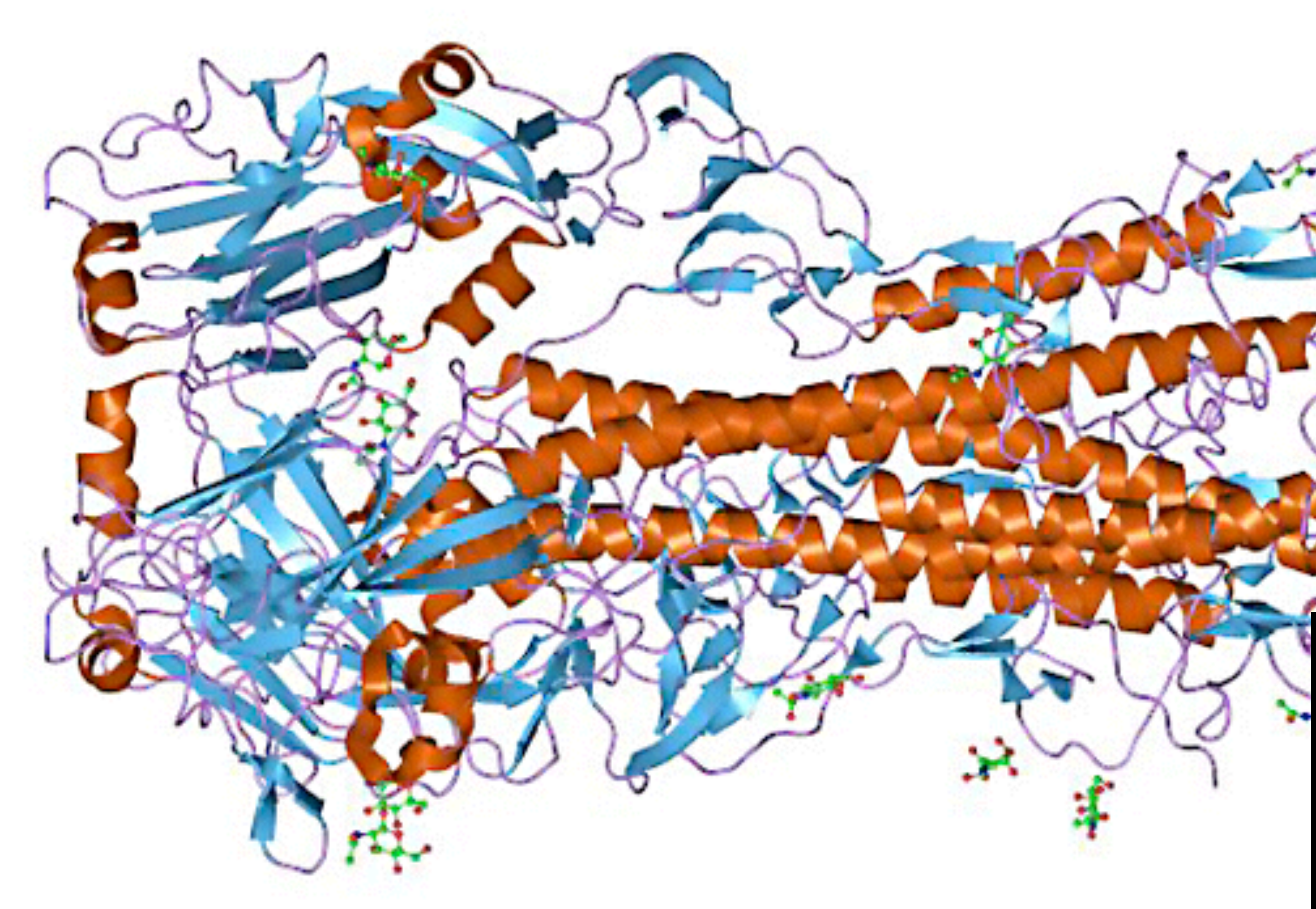
SciLifeLab

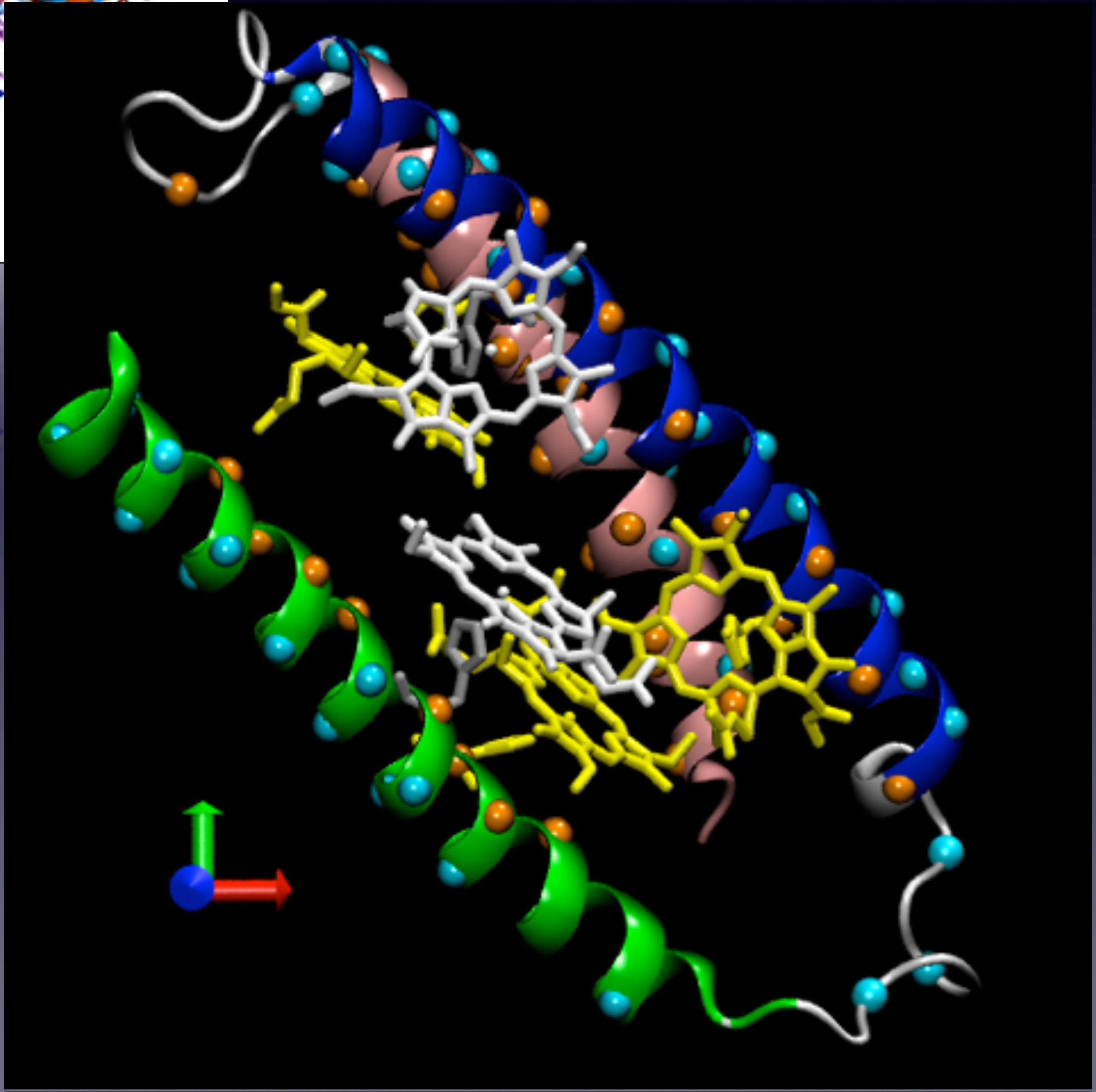
KTH VETENSKAP OCH KONST

STOCKHOLMS UNIVERSITET

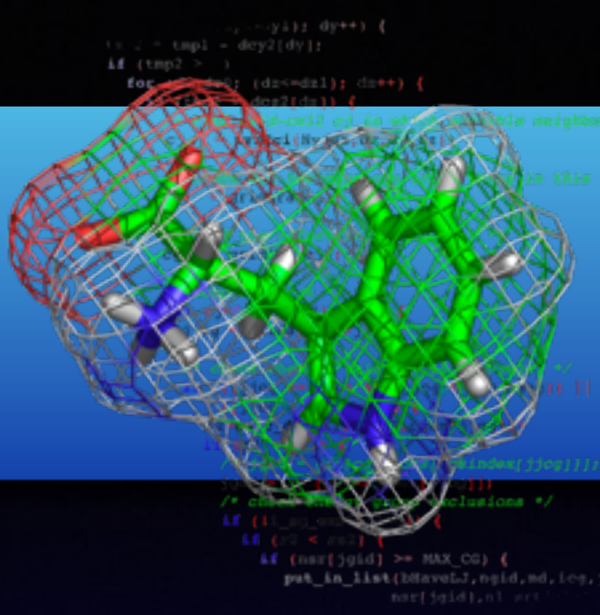

intracellular
N
A
P
D426
Cu+
M2
MA
M6
M4
C382
M717
E189
M5
MB
M1
M3
extracellular





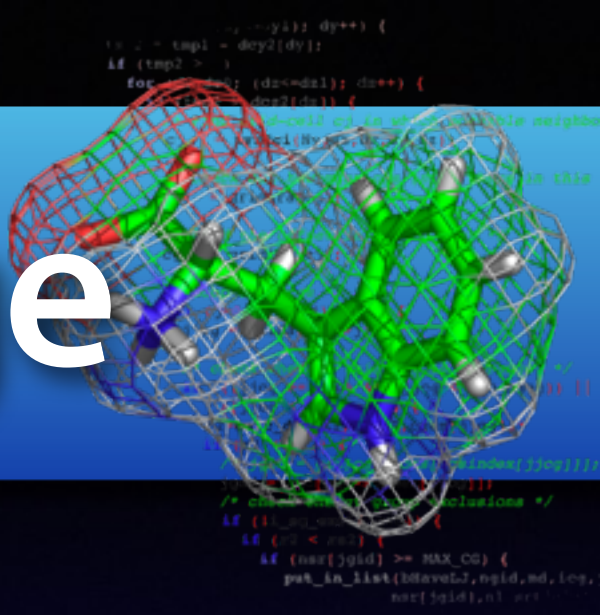


Protein Physics



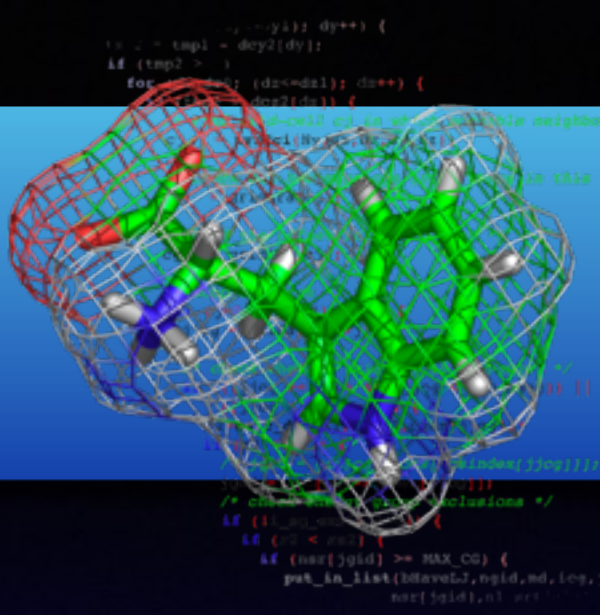
- Understanding protein structure & stability
- Understanding protein folding
- Sequence-structure-function
- Predicting protein structure
- Engineering protein structure
- Mix of chemistry/biology/physics

Course homepage



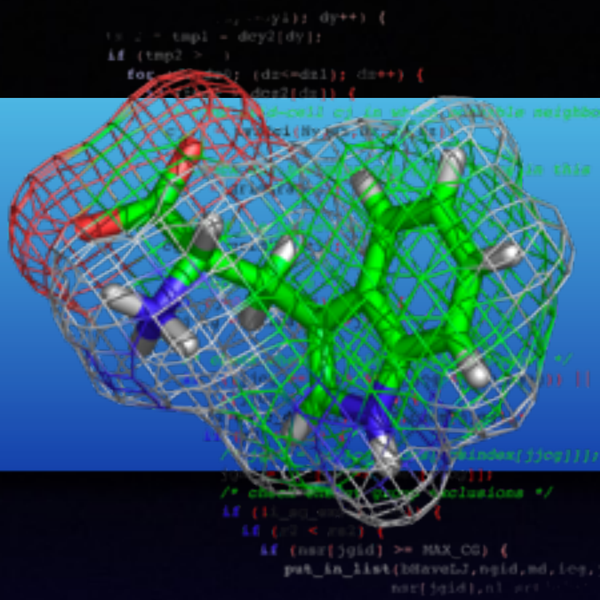
- http://courses.theophys.kth.se/SI2700/
- Full schedule with changes online asap
- Copies of slides, papers, etc. will be uploaded

Book



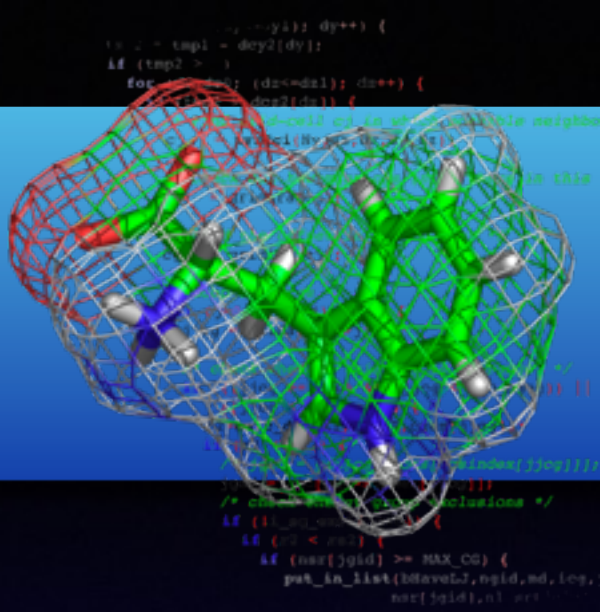
- “Protein Physics”
- Alexei Finkelstein & Oleg Ptitsyn
- ISBN 0-12-256781-1
- Can be a bit hard to get, try online
- Extra reading material will be handed out

Assessment



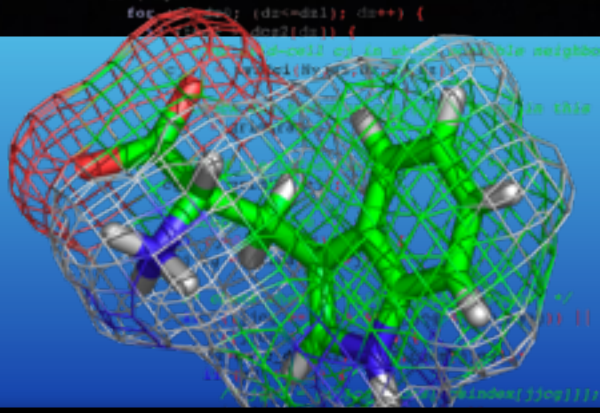
- There will be 2 hand-in tasks (pass/fail)
- 2-part written exam (E, D-A)
- Reports must be passed before taking the exam
- Pass on 2 hand-in task + 70% on E-part = E
- D-A decided by rest of written exam

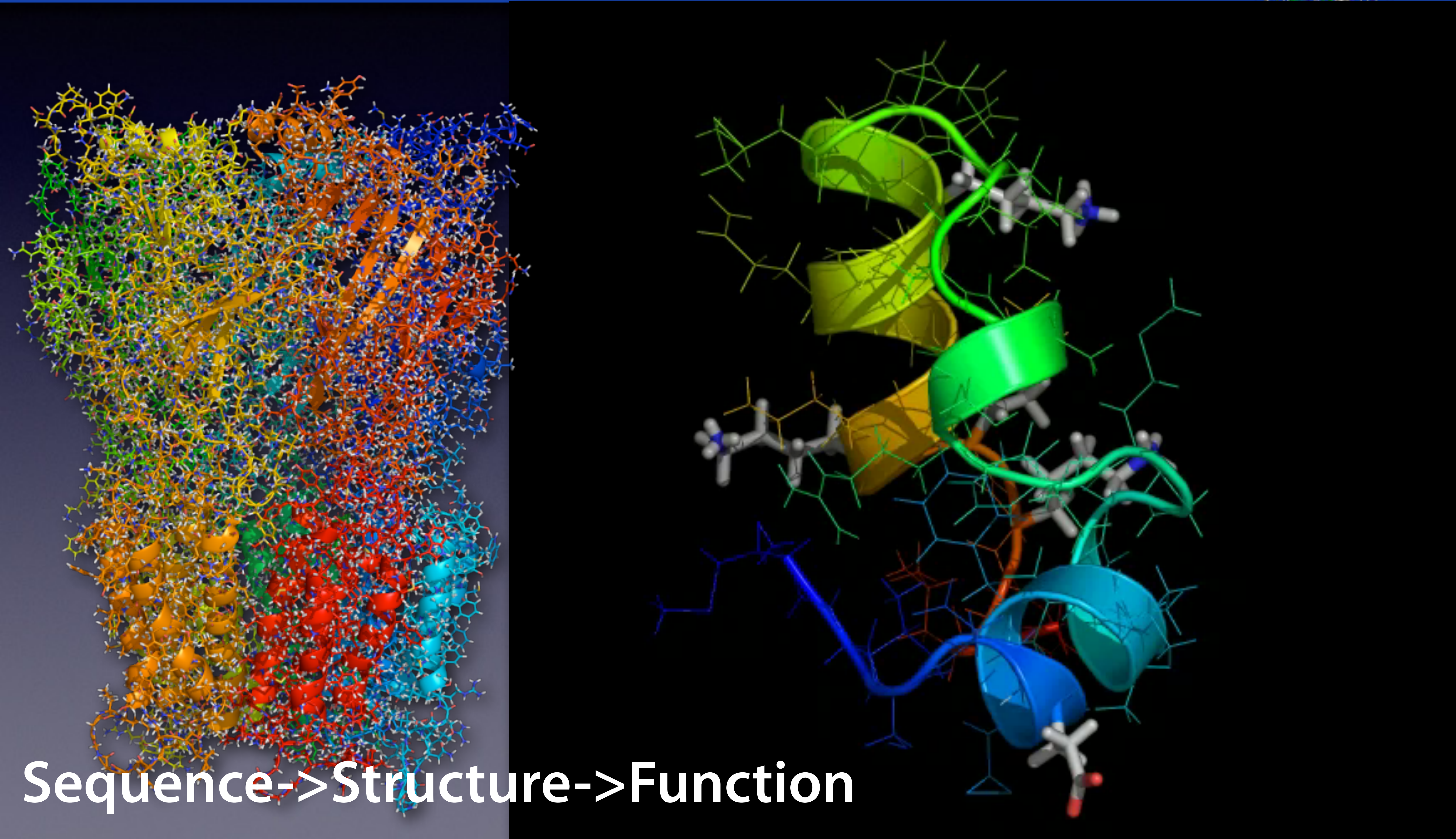
Outline today



- Basic concepts - possibly repetition for some
- Amino acids, proteins
- Basic physical properties of aa & proteins
- Structure of proteins, protein folding
- Elementary interactions in proteins
- Introduction to entropy, phase transitions

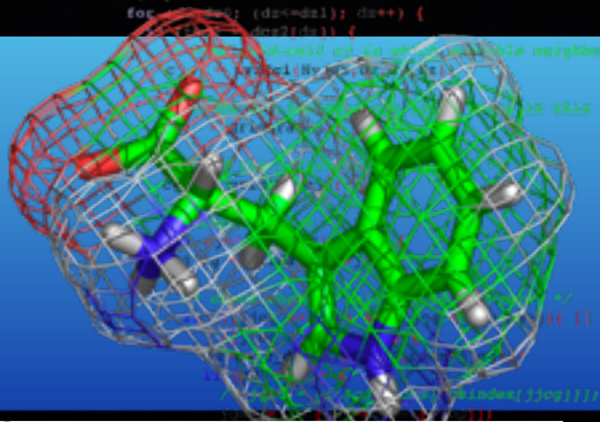
Protein structure

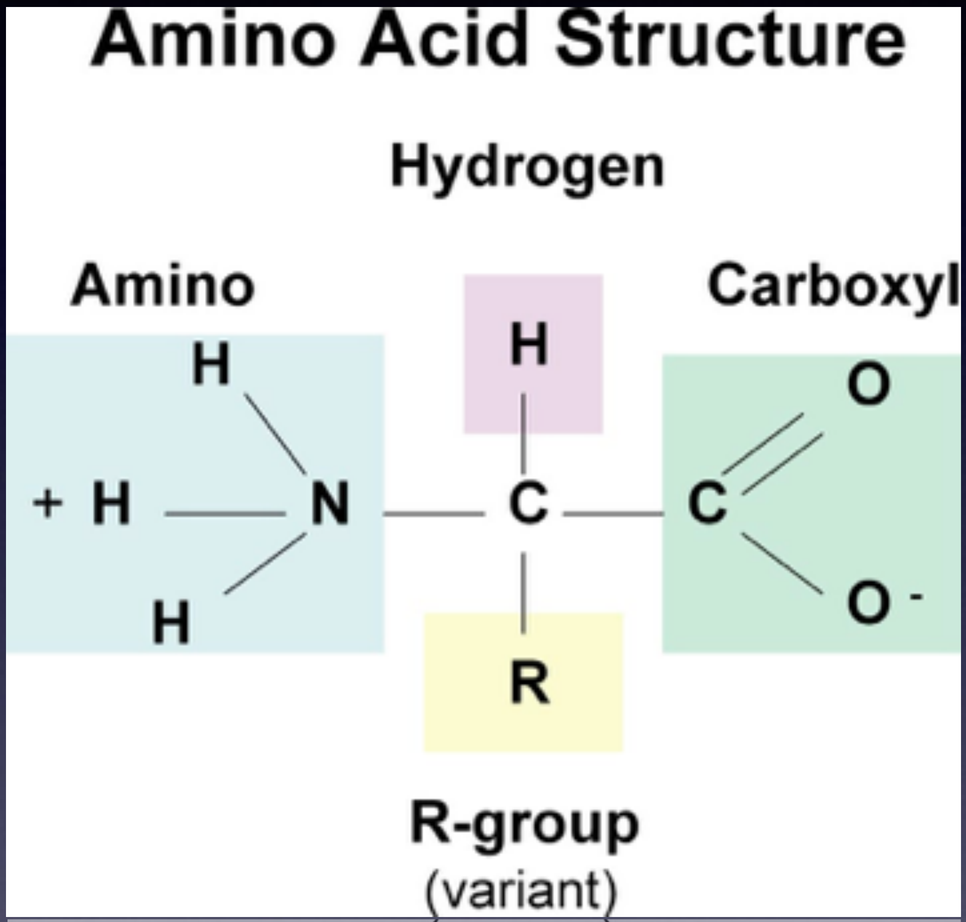




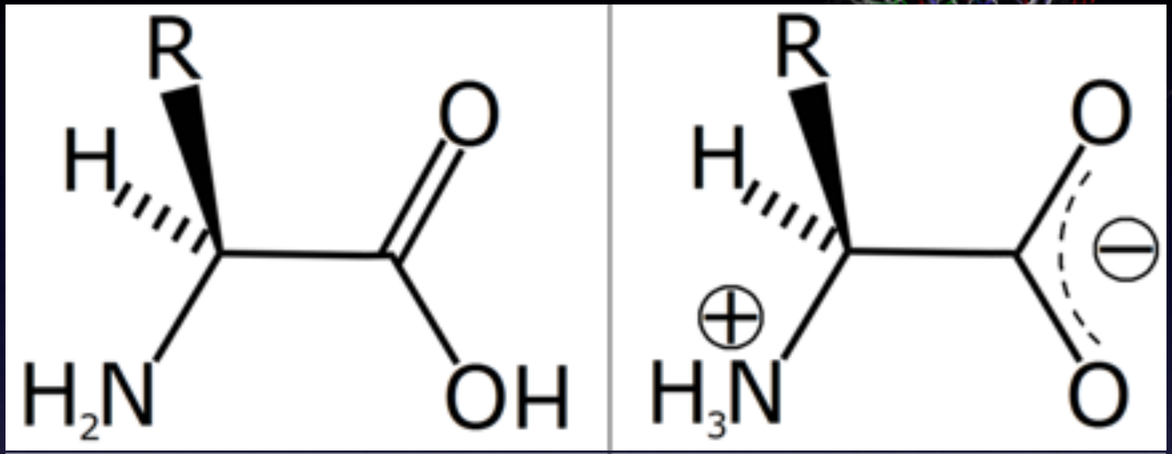
Sequence->Structure->Function

Amino acids

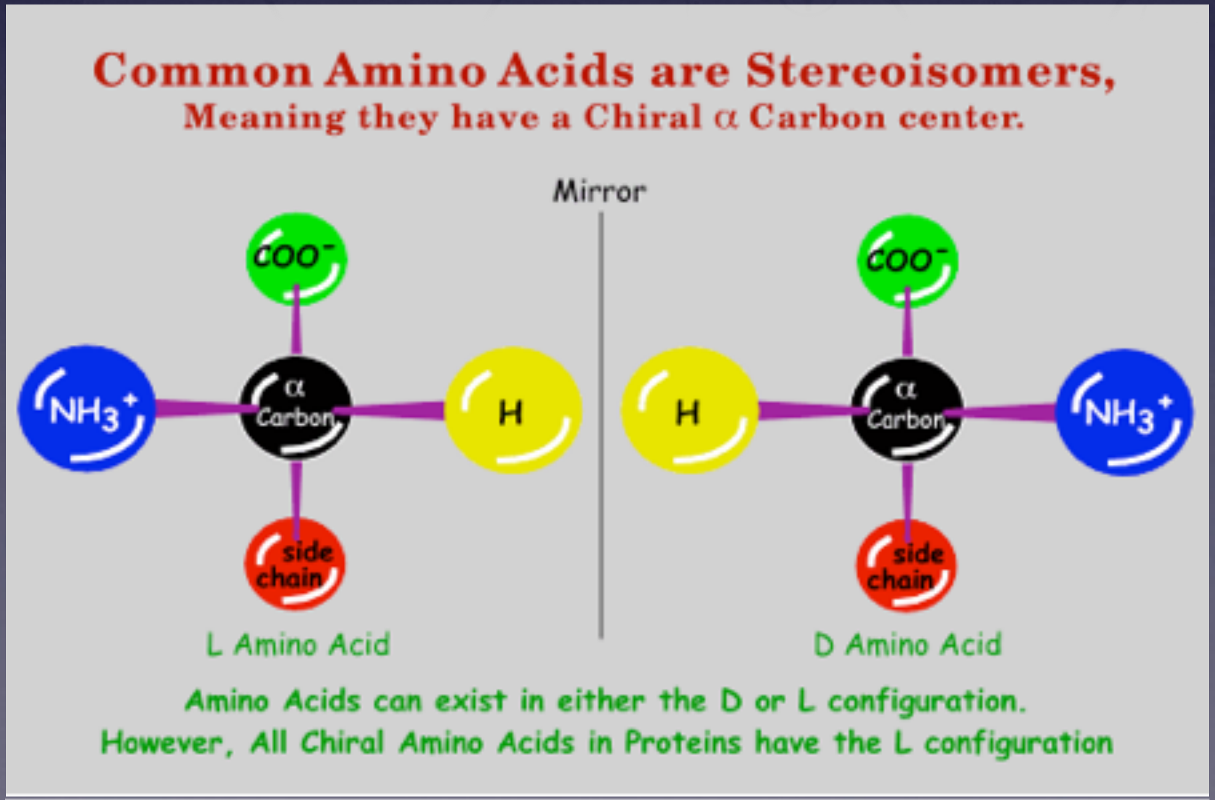




different properties



zwitterionic

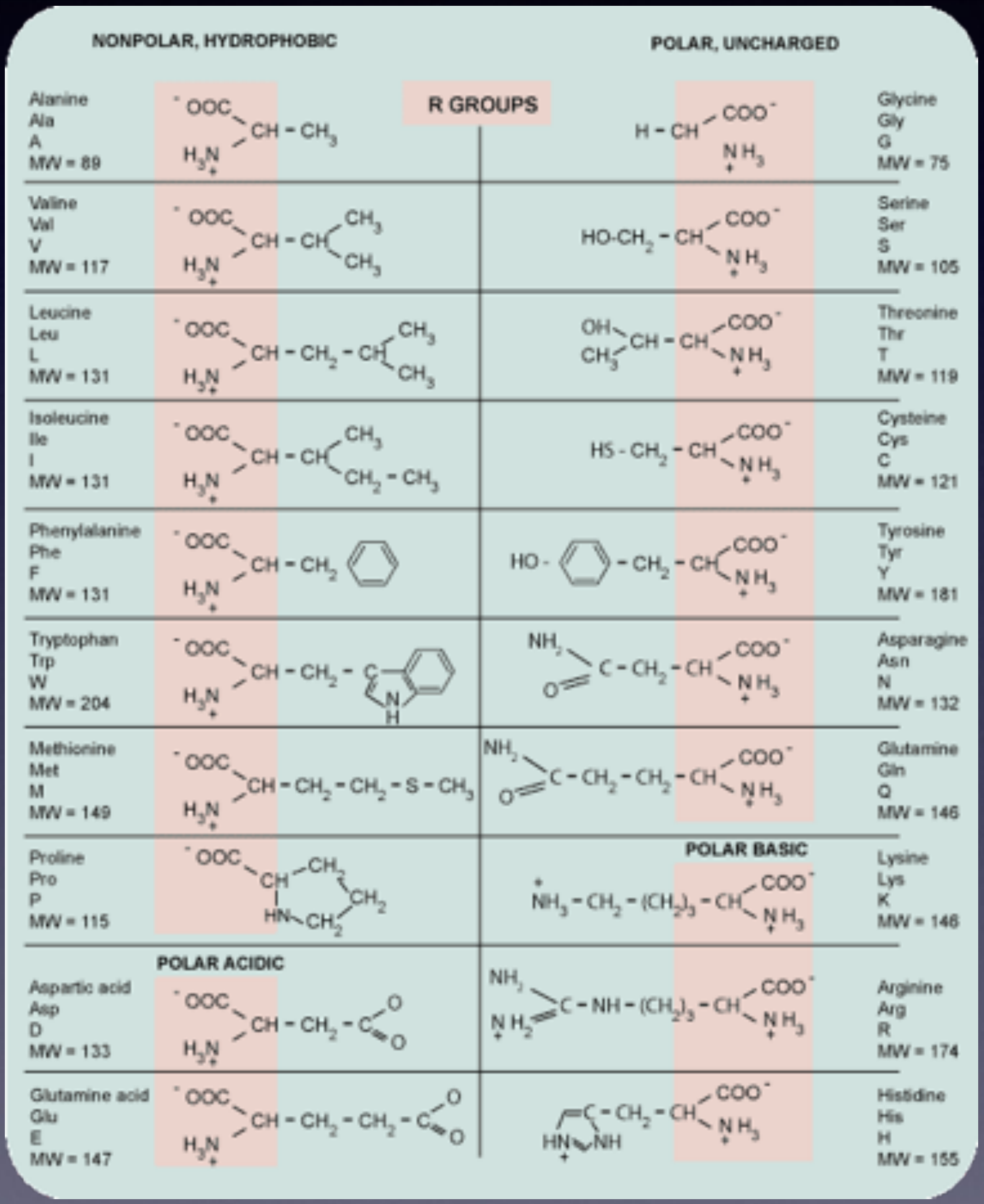


Common Amino Acids are Stereoisomers,
Meaning they have a Chiral α Carbon center.

Amino Acids can exist in either the D or L configuration.
However, All Chiral Amino Acids in Proteins have the L configuration

19 out of 20 are chiral: natural state is L!

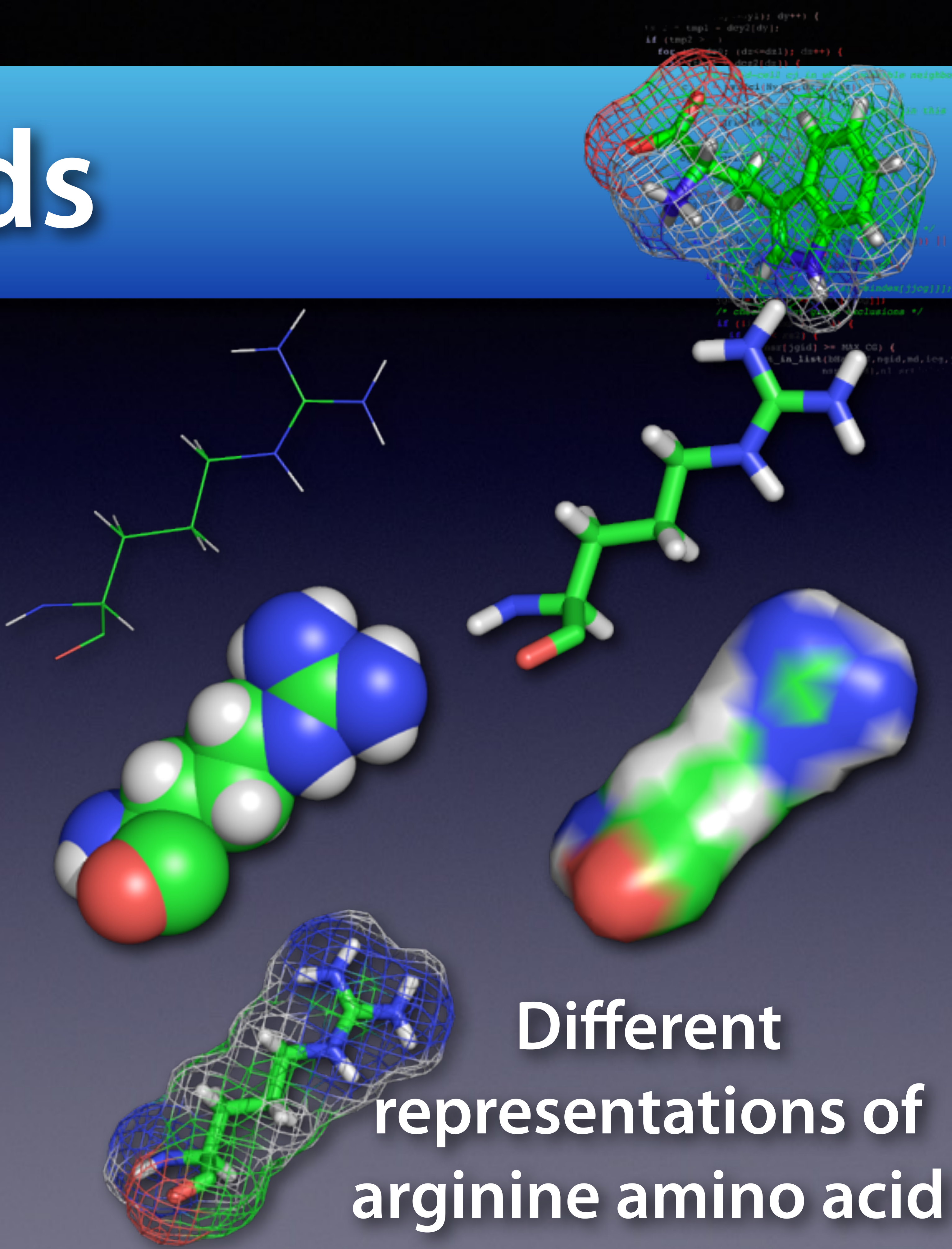
Amino acids



NONPOLAR, HYDROPHOBIC | **R GROUPS** | **POLAR, UNCHARGED**

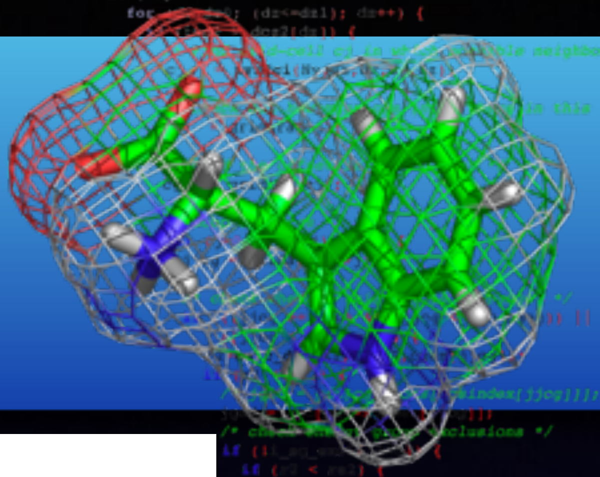
NONPOLAR, HYDROPHOBIC	POLAR, UNCHARGED
Alanine Ala A MW = 89	Glycine Gly G MW = 75
Valine Val V MW = 117	Serine Ser S MW = 105
Leucine Leu L MW = 131	Threonine Thr T MW = 119
Isoleucine Ile I MW = 131	Cysteine Cys C MW = 121
Phenylalanine Phe F MW = 131	Tyrosine Tyr Y MW = 181
Tryptophan Trp W MW = 204	Asparagine Asn N MW = 132
Methionine Met M MW = 149	Glutamine Gln Q MW = 146
Proline Pro P MW = 115	**POLAR BASIC** Lysine Lys K MW = 146
POLAR ACIDIC Aspartic acid Asp D MW = 133	Arginine Arg R MW = 174
Glutamine acid Glu E MW = 147	Histidine His H MW = 155

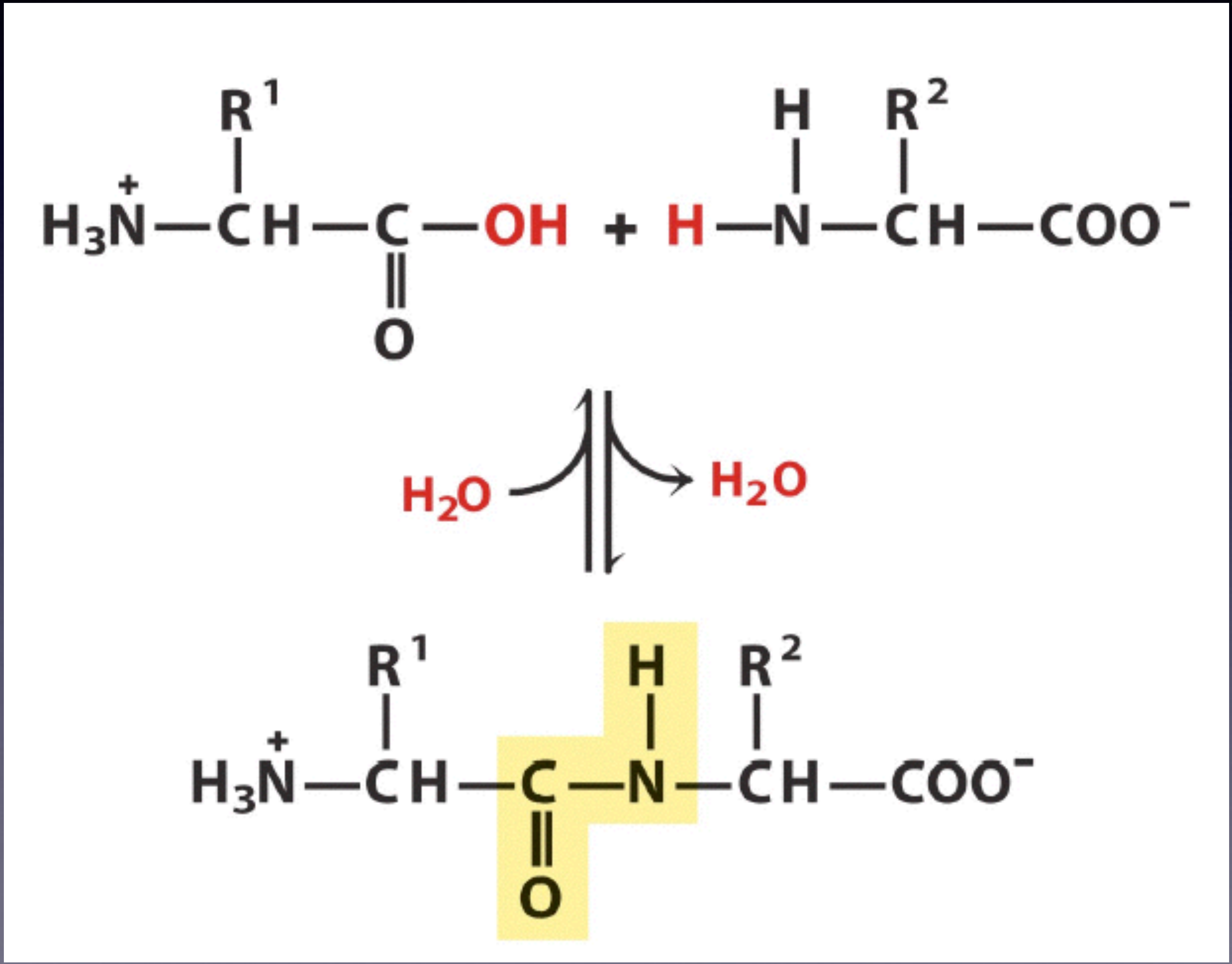
atomic vs molecular levels



Different representations of arginine amino acid

Polymerization



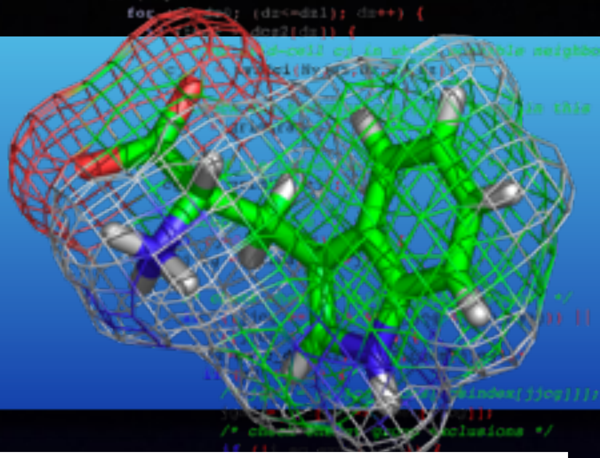


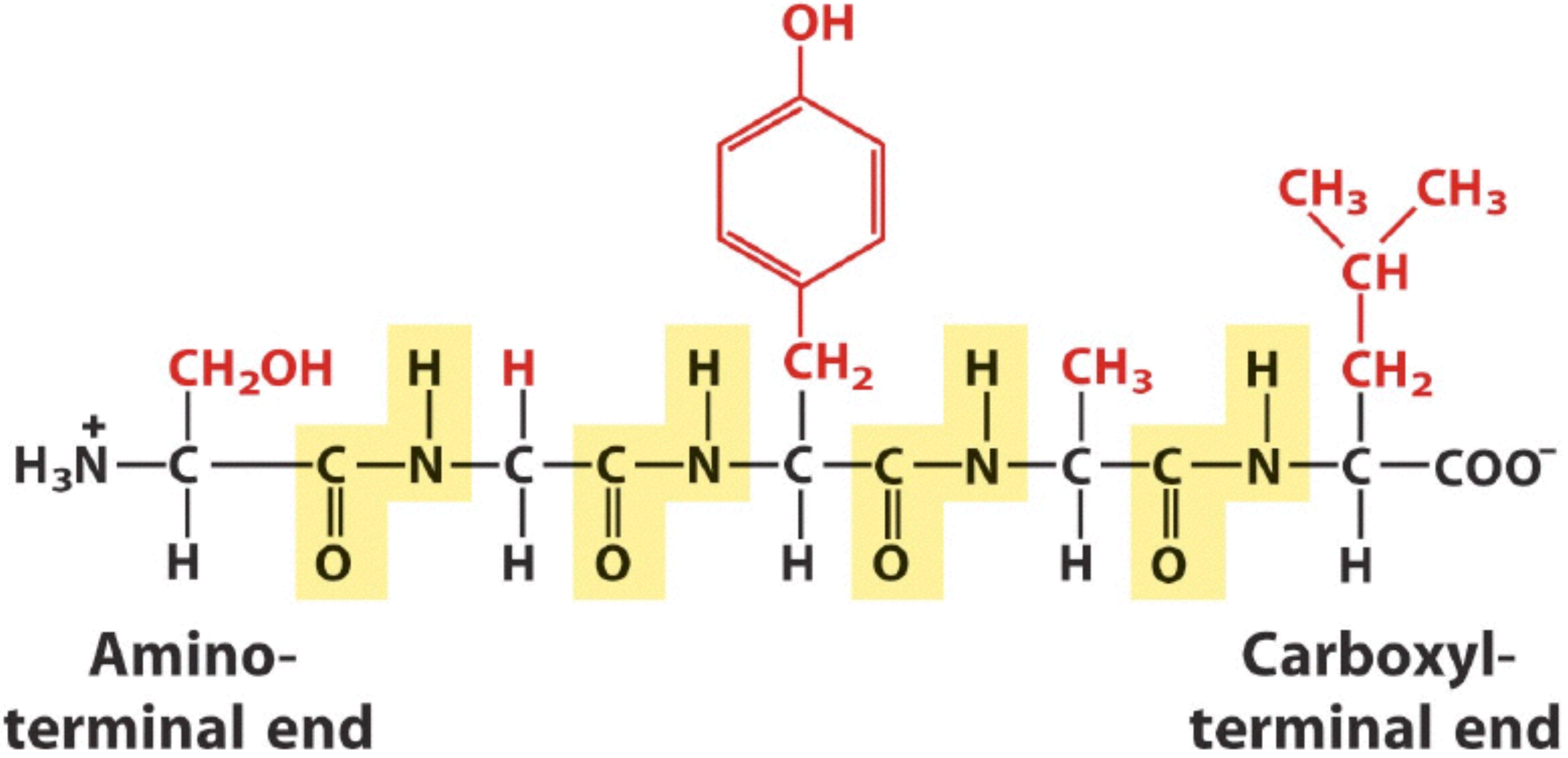
$$\mathrm{H_3\overset{+}{N}-\overset{\displaystyle R^1}{\overset{|}{C}H}-\underset{\displaystyle O}{\underset{\|}{C}}-OH + H-\overset{\displaystyle H}{\overset{|}{N}}-\overset{\displaystyle R^2}{\overset{|}{C}H}-COO^-}$$

$$\xrightarrow{H_2O}\!\!\!\!\!\!\!\!\!\!\!\!\!\xleftarrow{H_2O}$$

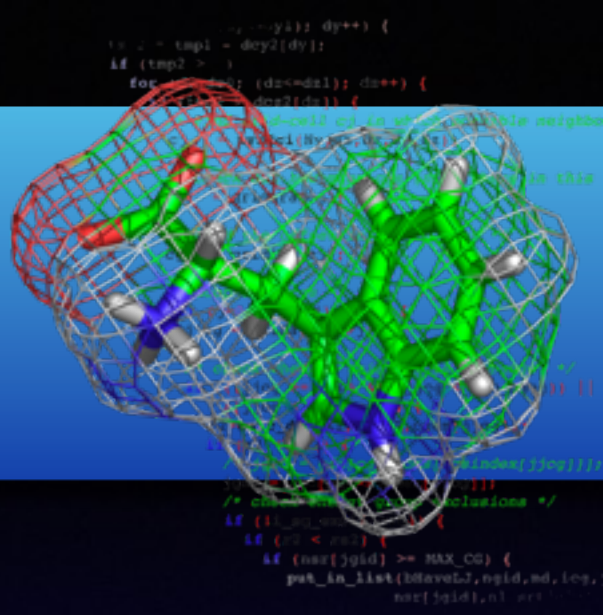
$$\mathrm{H_3\overset{+}{N}-\overset{\displaystyle R^1}{\overset{|}{C}H}-\underset{\displaystyle O}{\underset{\|}{C}}-\overset{\displaystyle H}{\overset{|}{N}}-\overset{\displaystyle R^2}{\overset{|}{C}H}-COO^-}$$

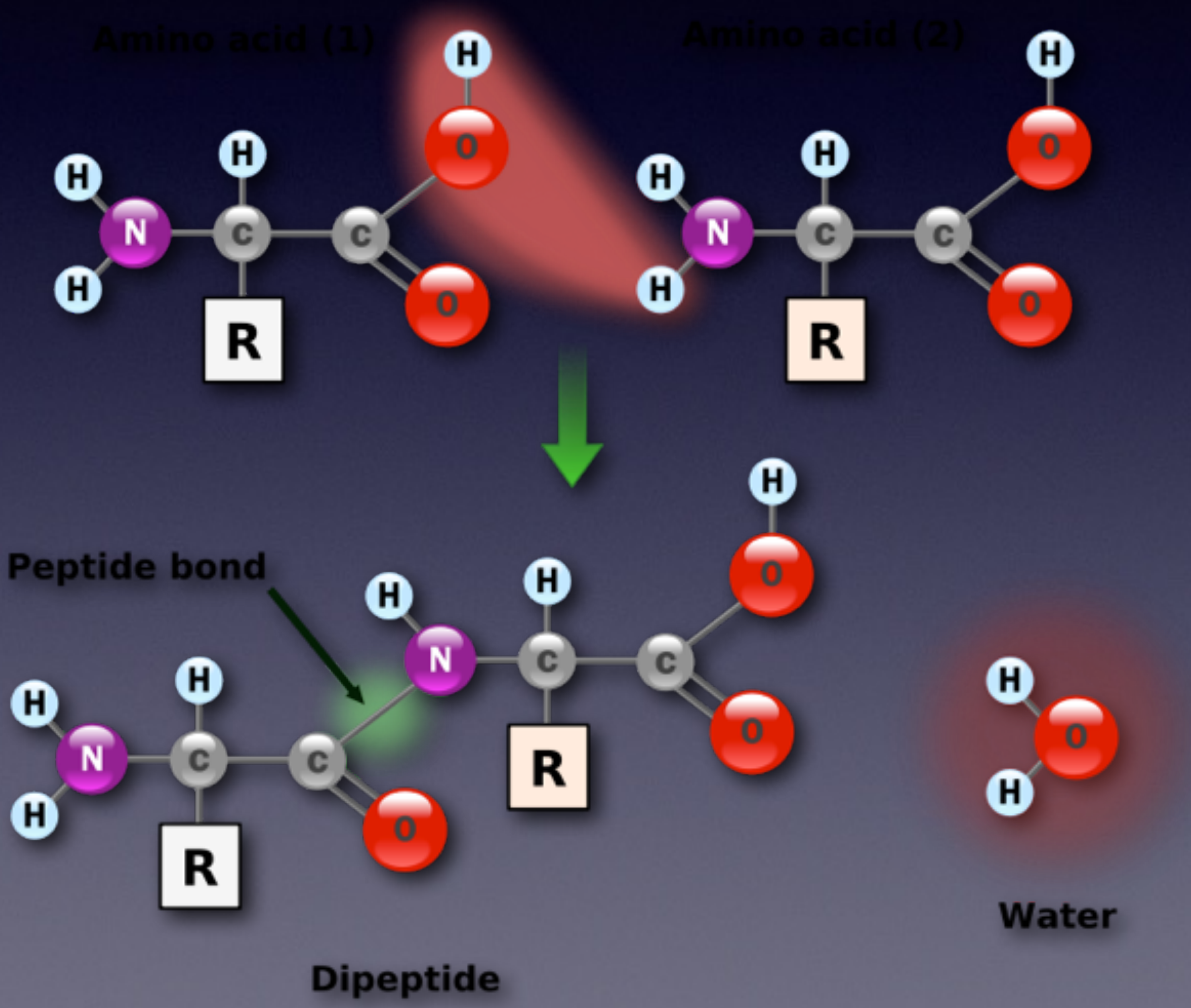
Polypeptides





Peptide bonds

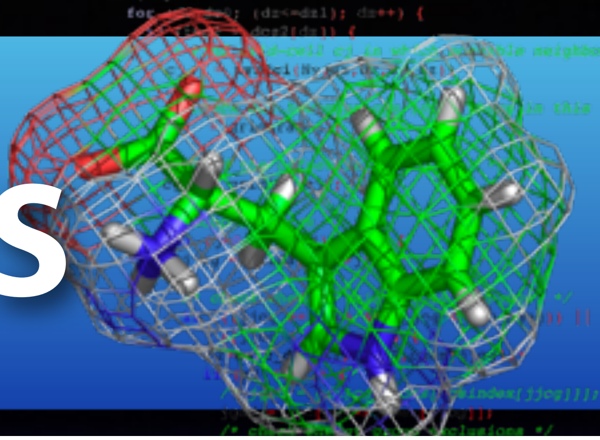




Peptide bond rigid & planar (sp2-hybridization, electron delocalized)

Peptide bond polarity

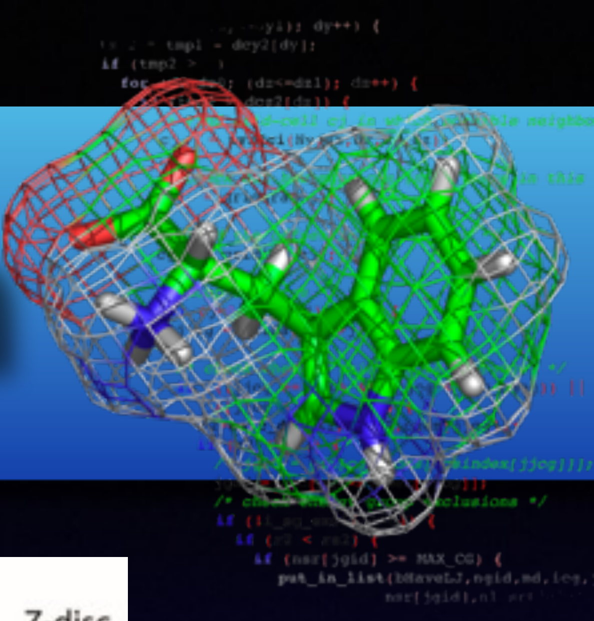
Example Proteins

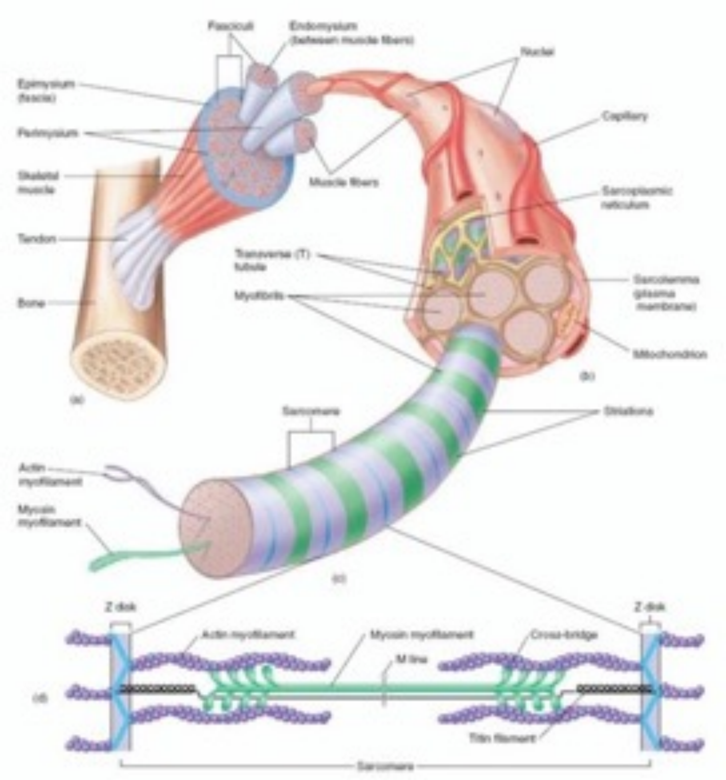


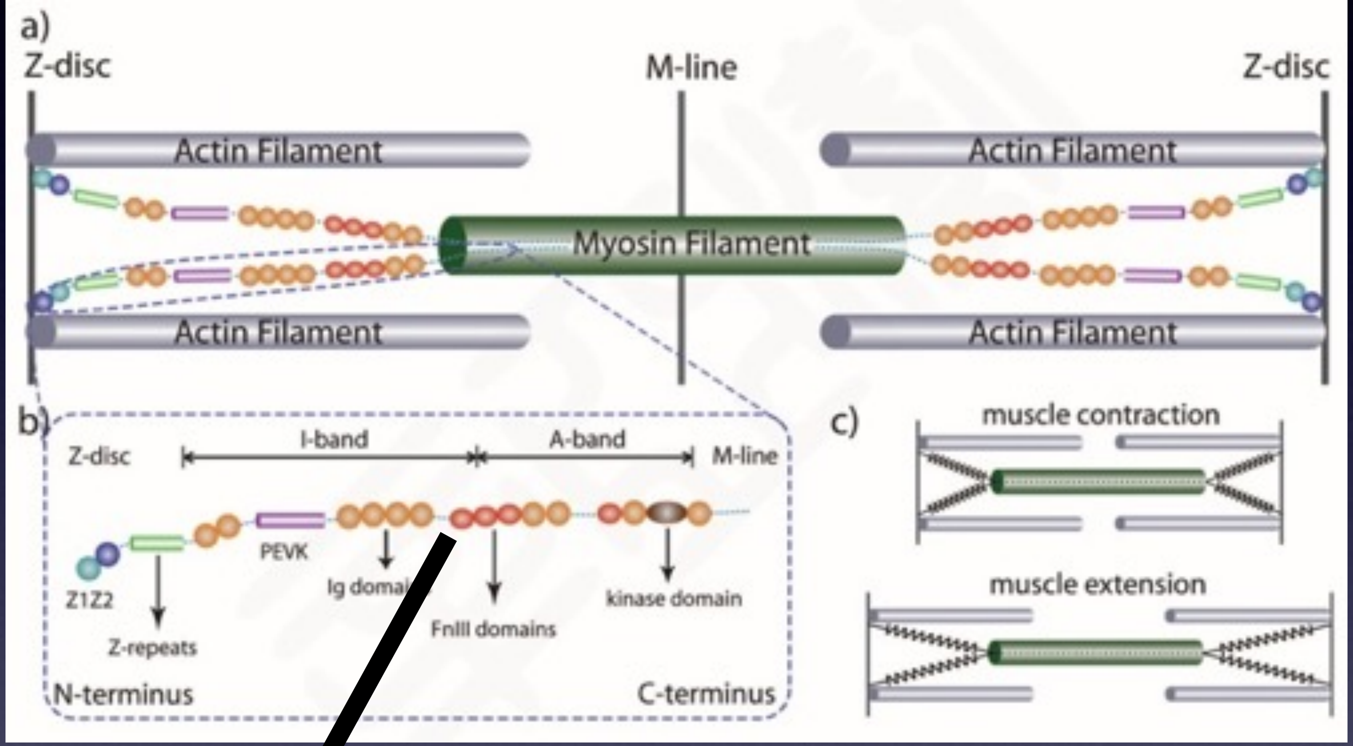
weight ~110 per amino acid

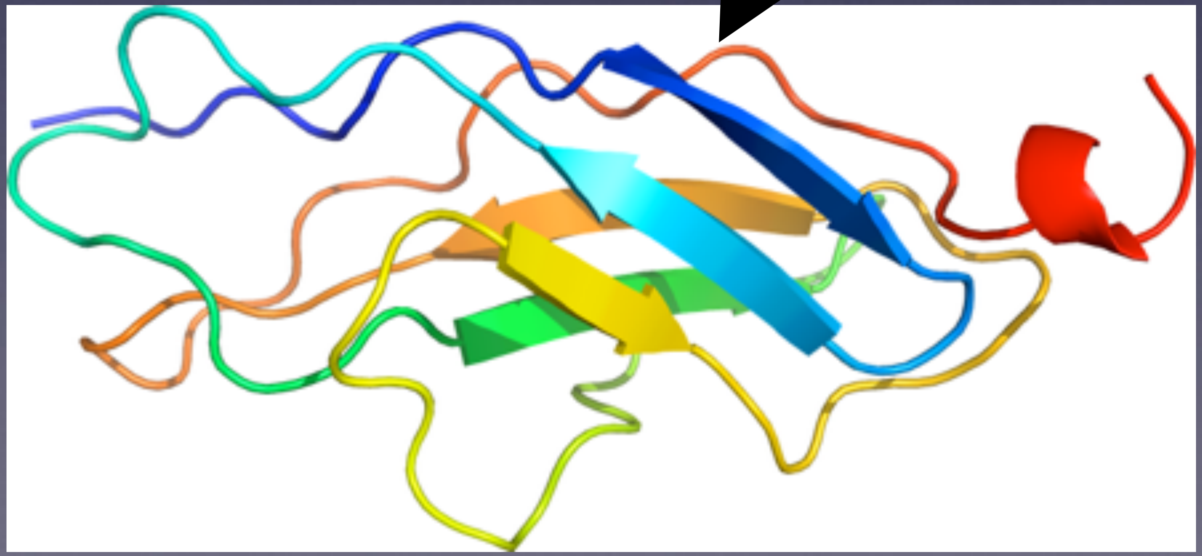
	Molecular weight	*Number of residues*	*Number of polypeptide chains*
Cytochrome *c* (human)	13,000	104	1
Ribonuclease A (bovine pancreas)	13,700	124	1
Lysozyme (chicken egg white)	13,930	129	1
Myoglobin (equine heart)	16,890	153	1
Chymotrypsin (bovine pancreas)	21,600	241	3
Chymotrypsinogen (bovine)	22,000	245	1
Hemoglobin (human)	64,500	574	4
Serum albumin (human)	68,500	609	1
Hexokinase (yeast)	102,000	972	2
RNA polymerase (*E. coli*)	450,000	4,158	5
Apolipoprotein B (human)	513,000	4,536	1
Glutamine synthetase (*E. coli*)	619,000	5,628	12
Titin (human)	2,993,000	26,926	1

Case study: Titin



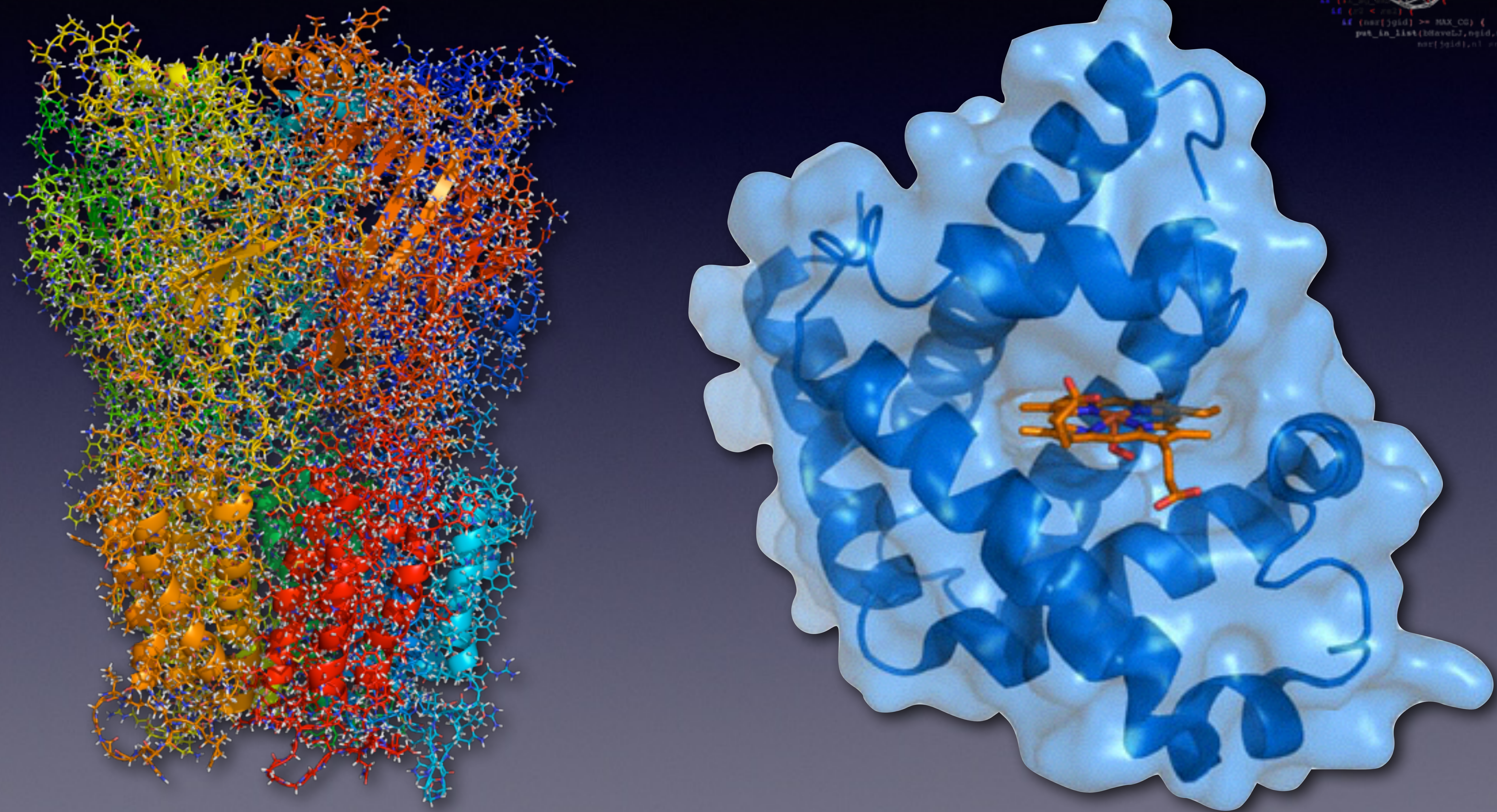




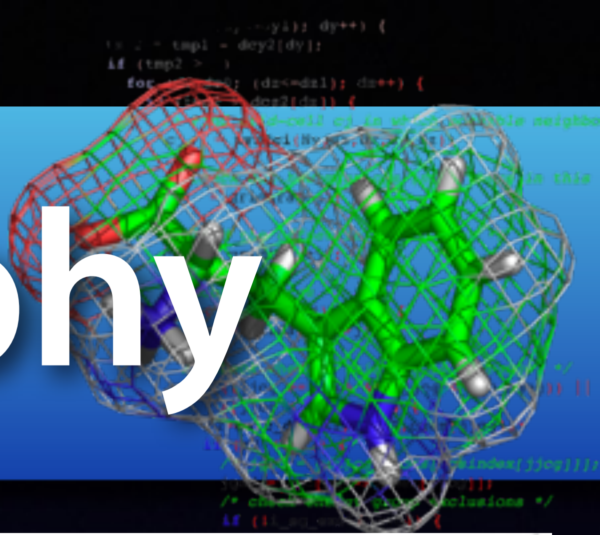


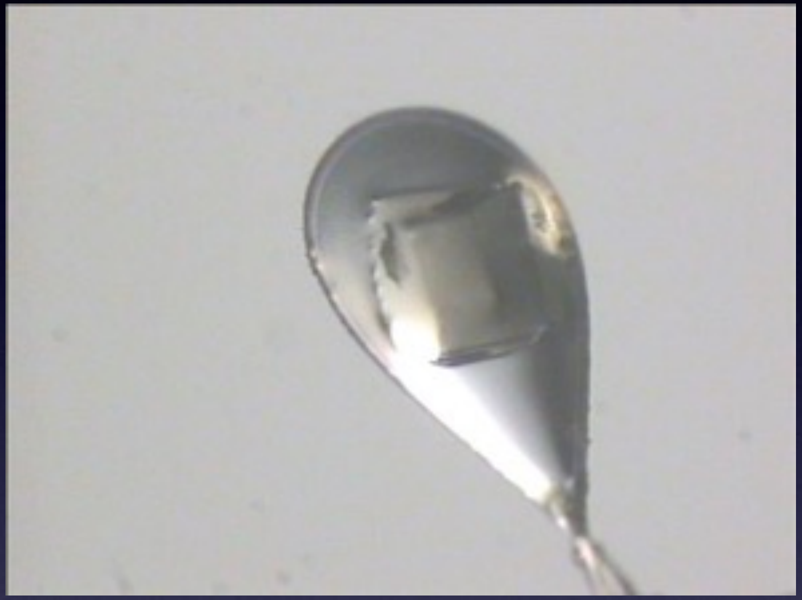
FnIII domain

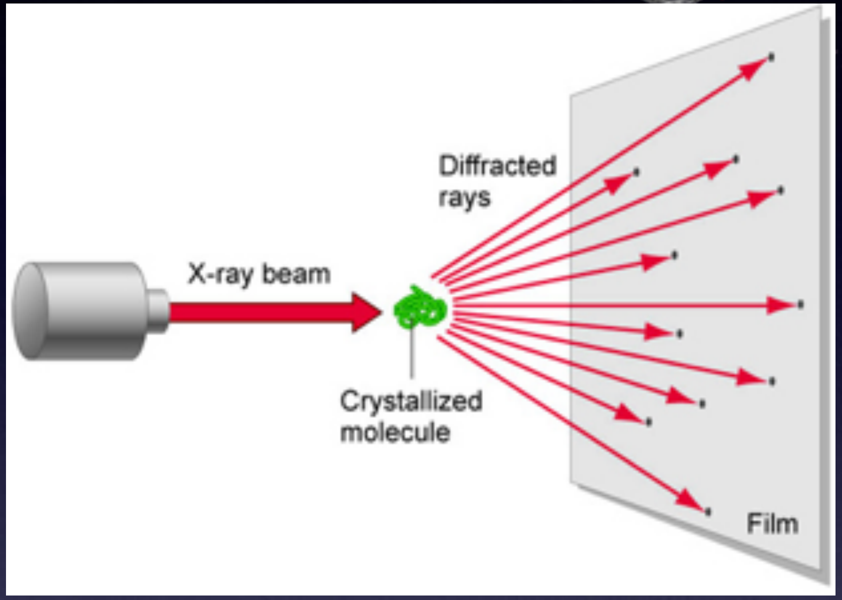
An assembled protein

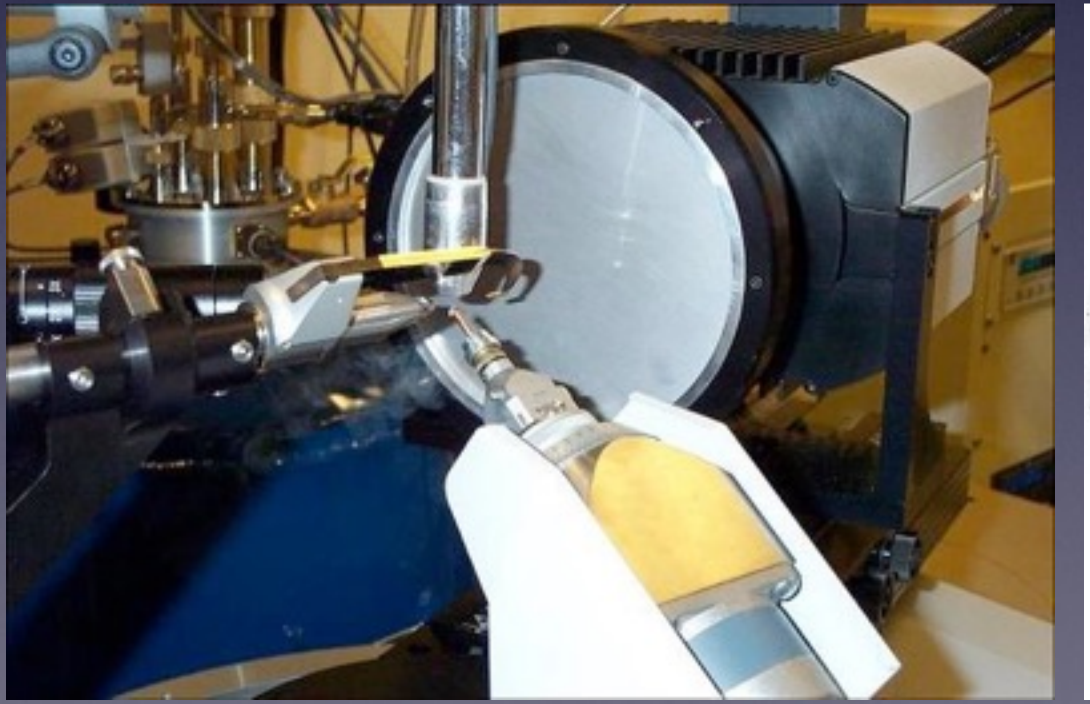


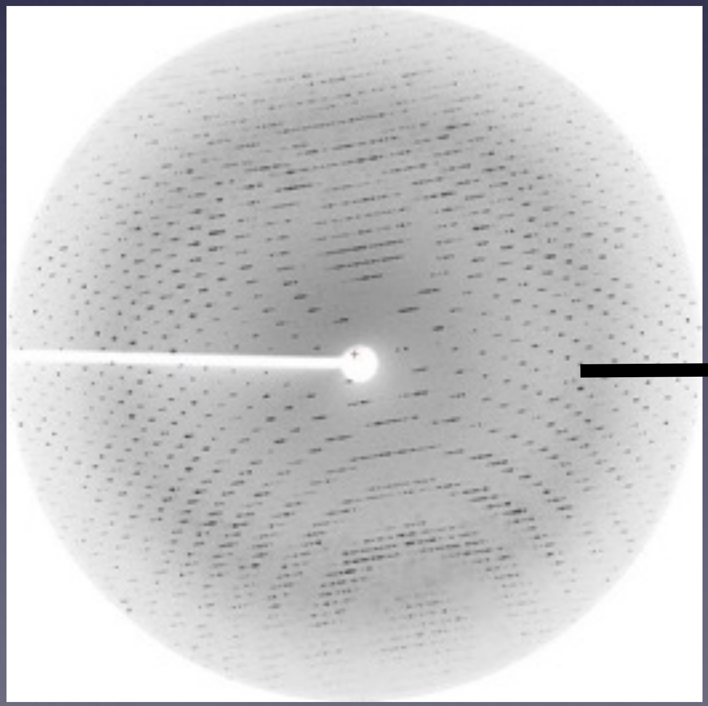
X-ray crystallography





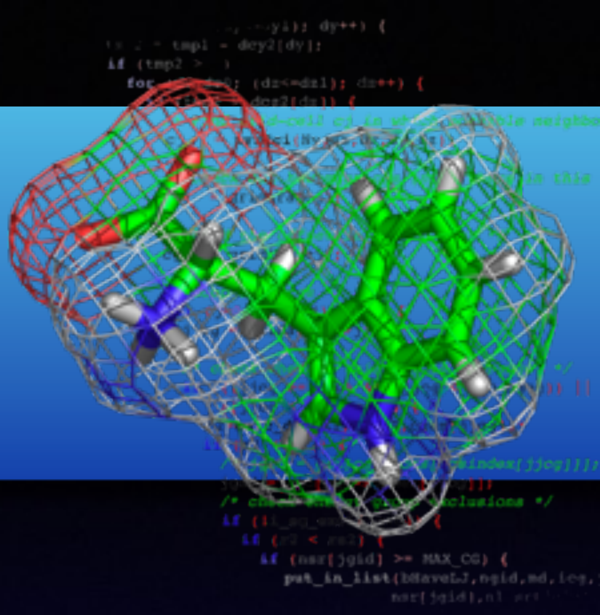




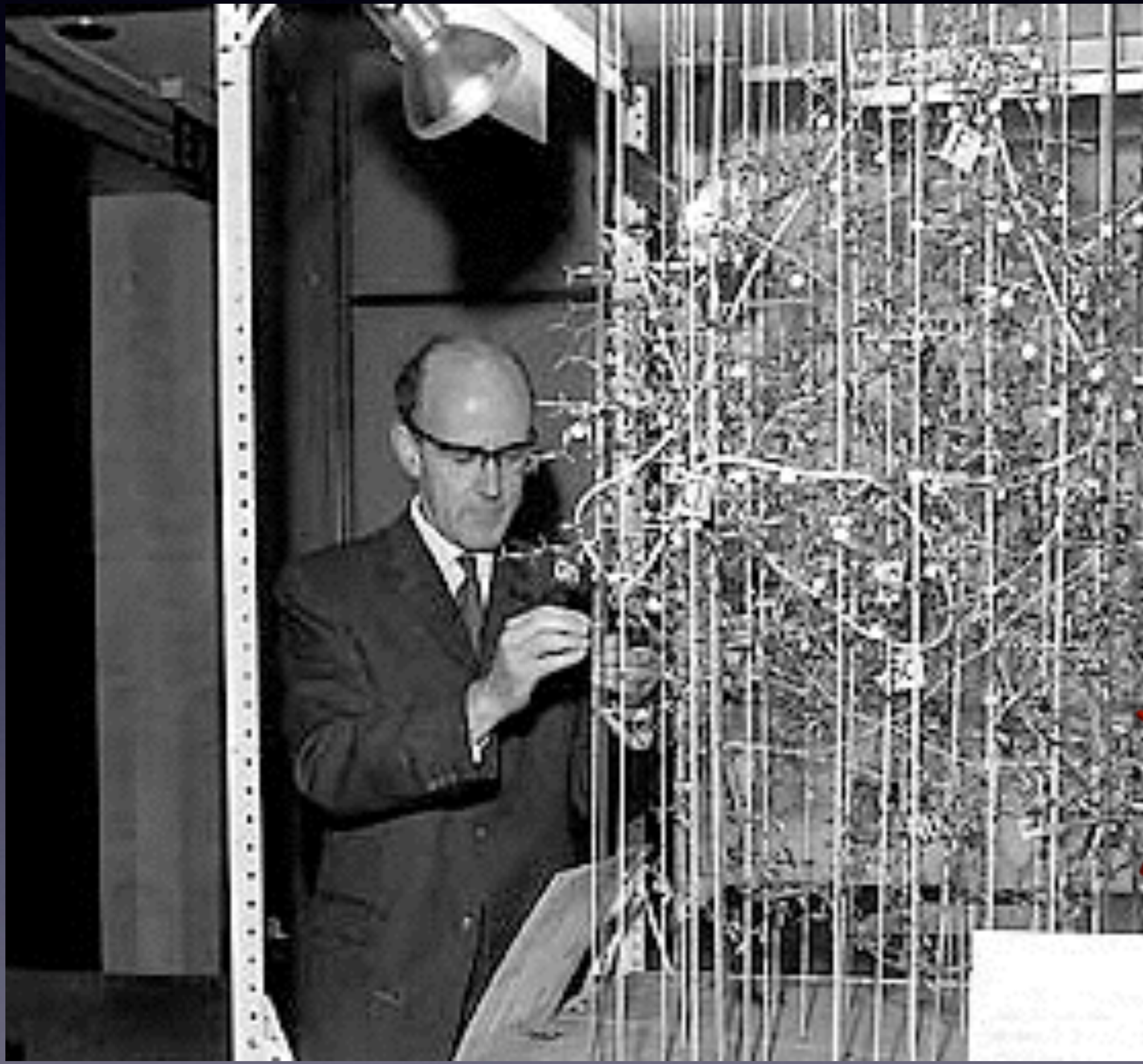


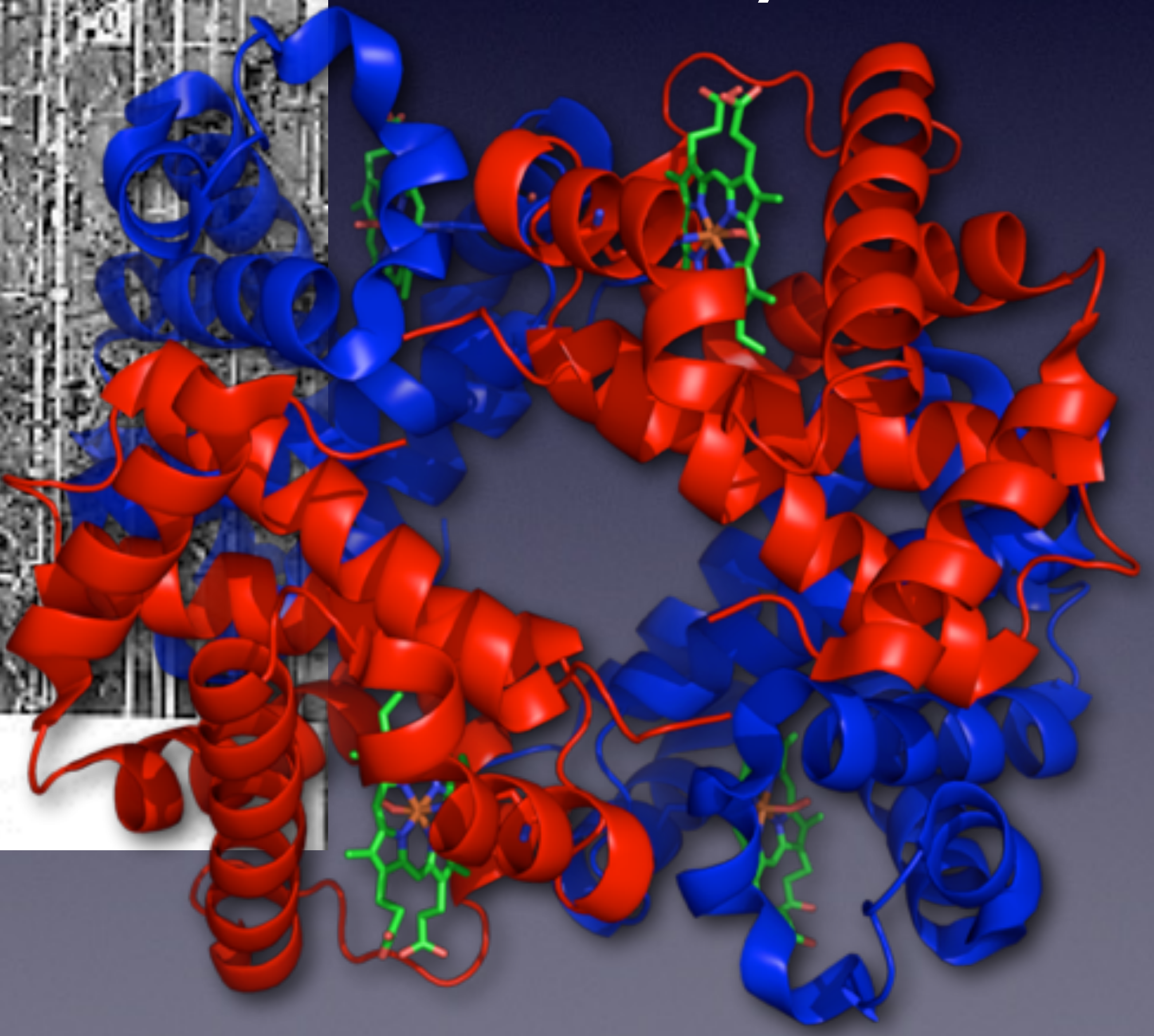
→ Protein structure

Protein structure



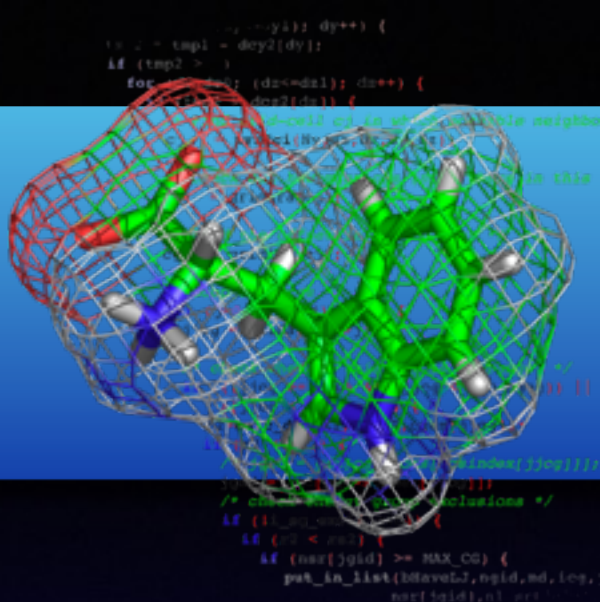
X-ray structure
Took 22 years...



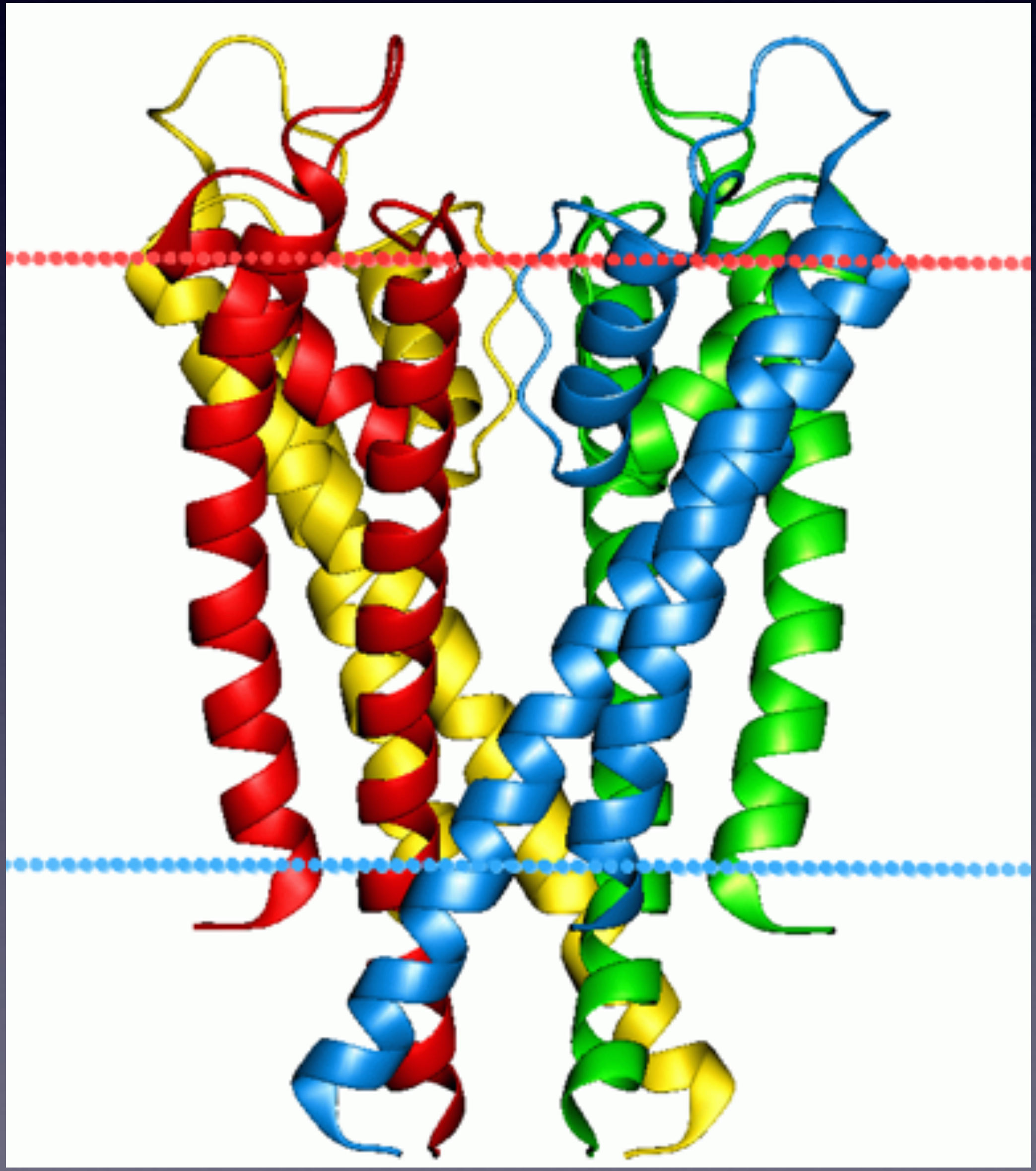


Max Perutz & Hemoglobin

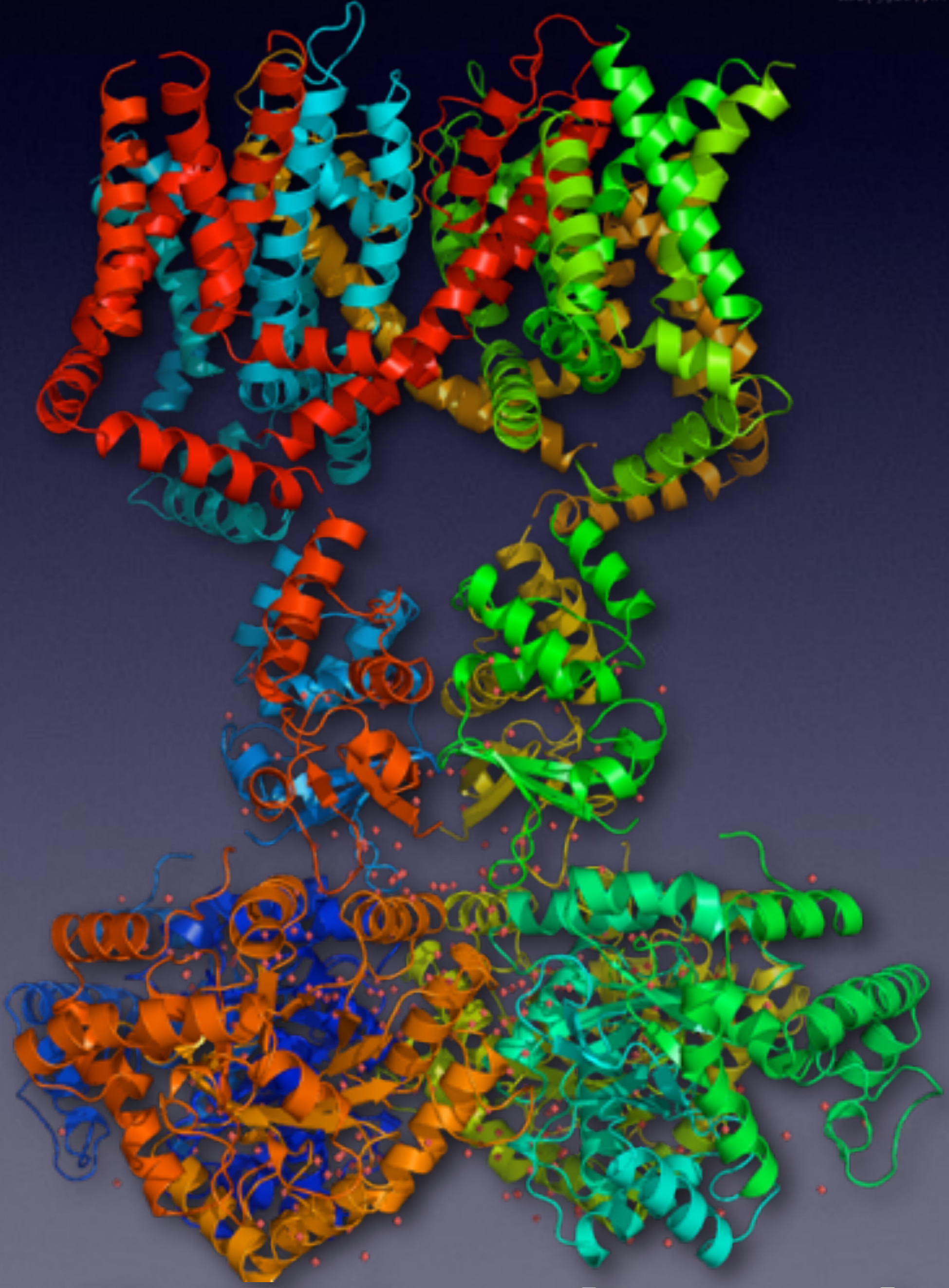
Protein structure



Rod MacKinnon - 2003

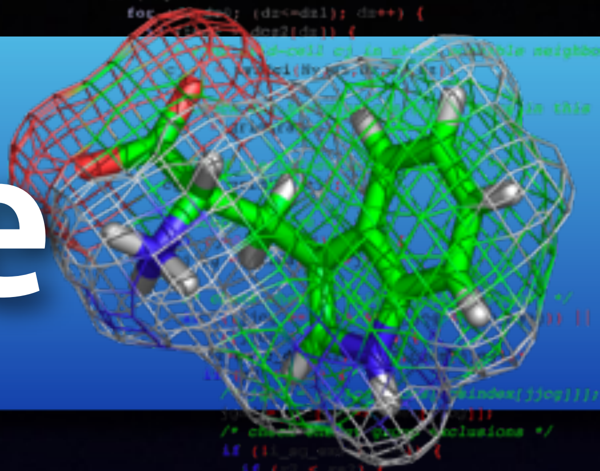


KcsA

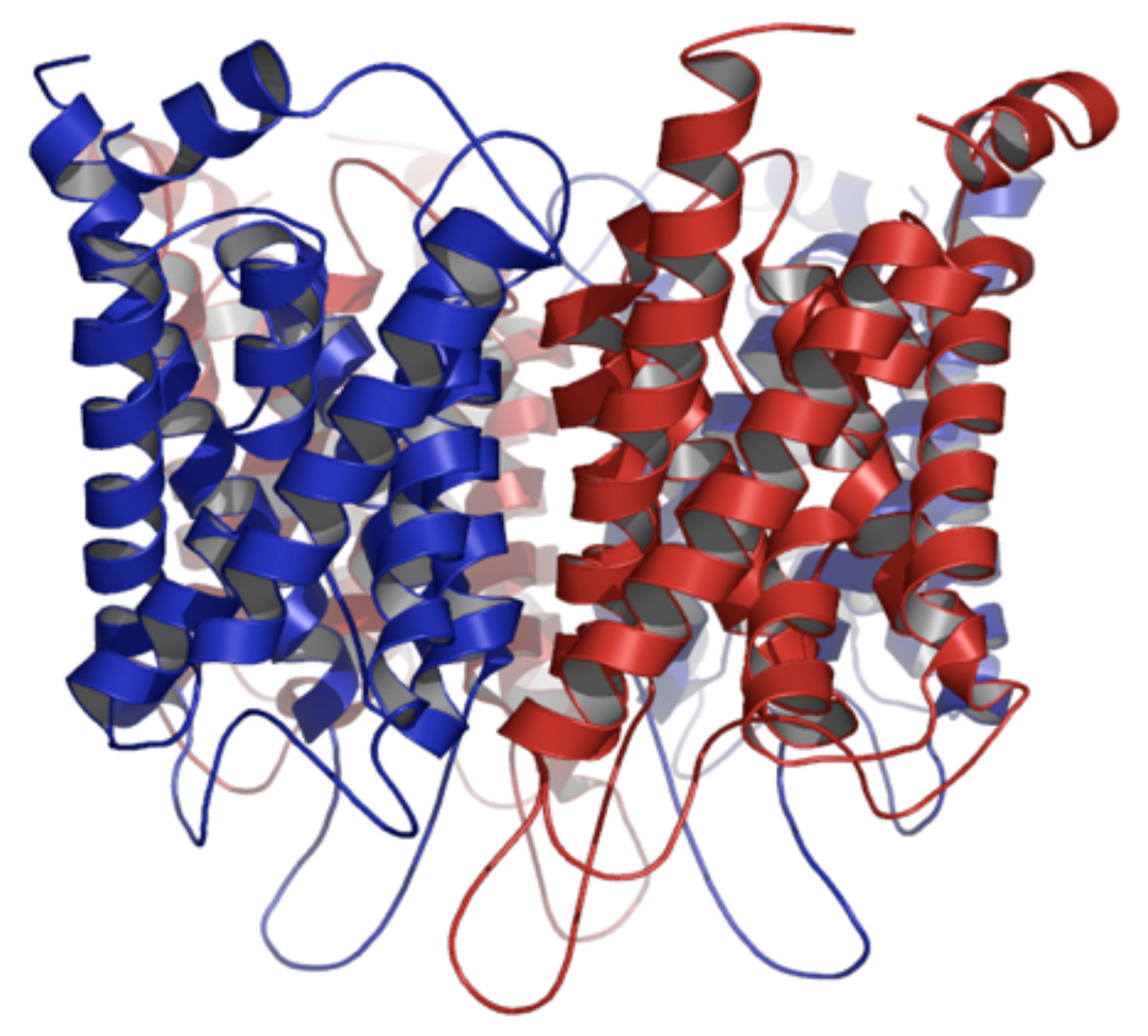


Kv1.2 ion channel

Protein structure

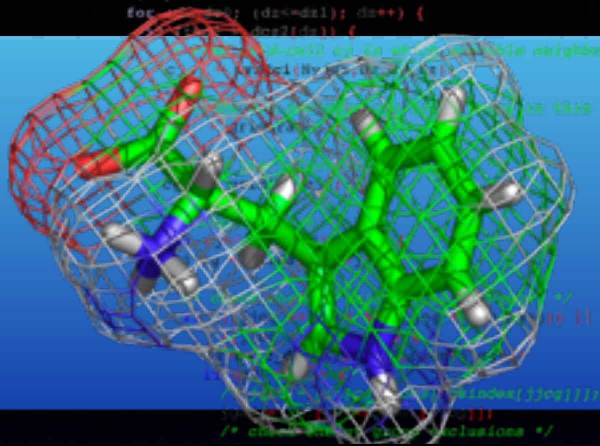


Peter Agre - 2003

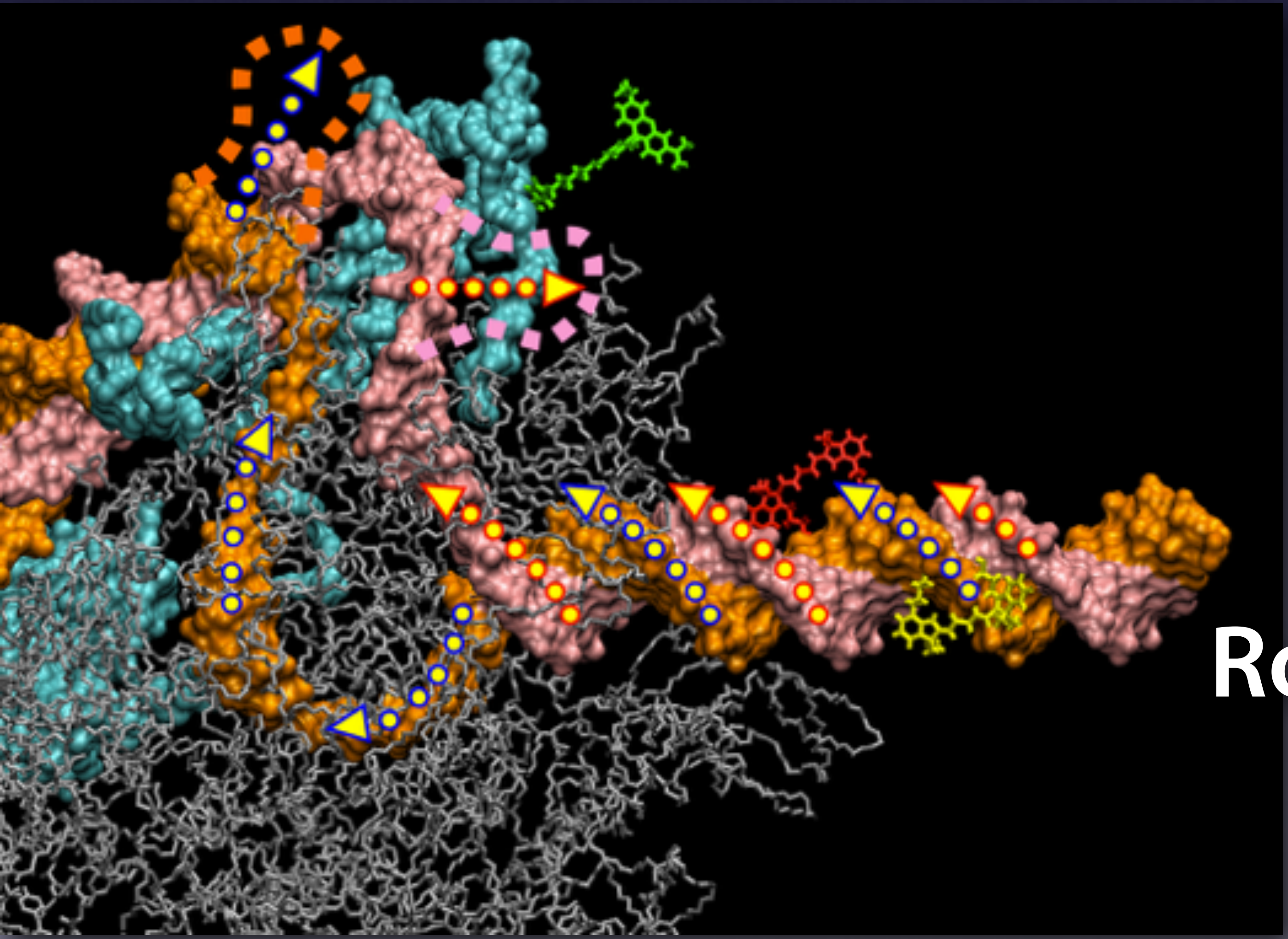


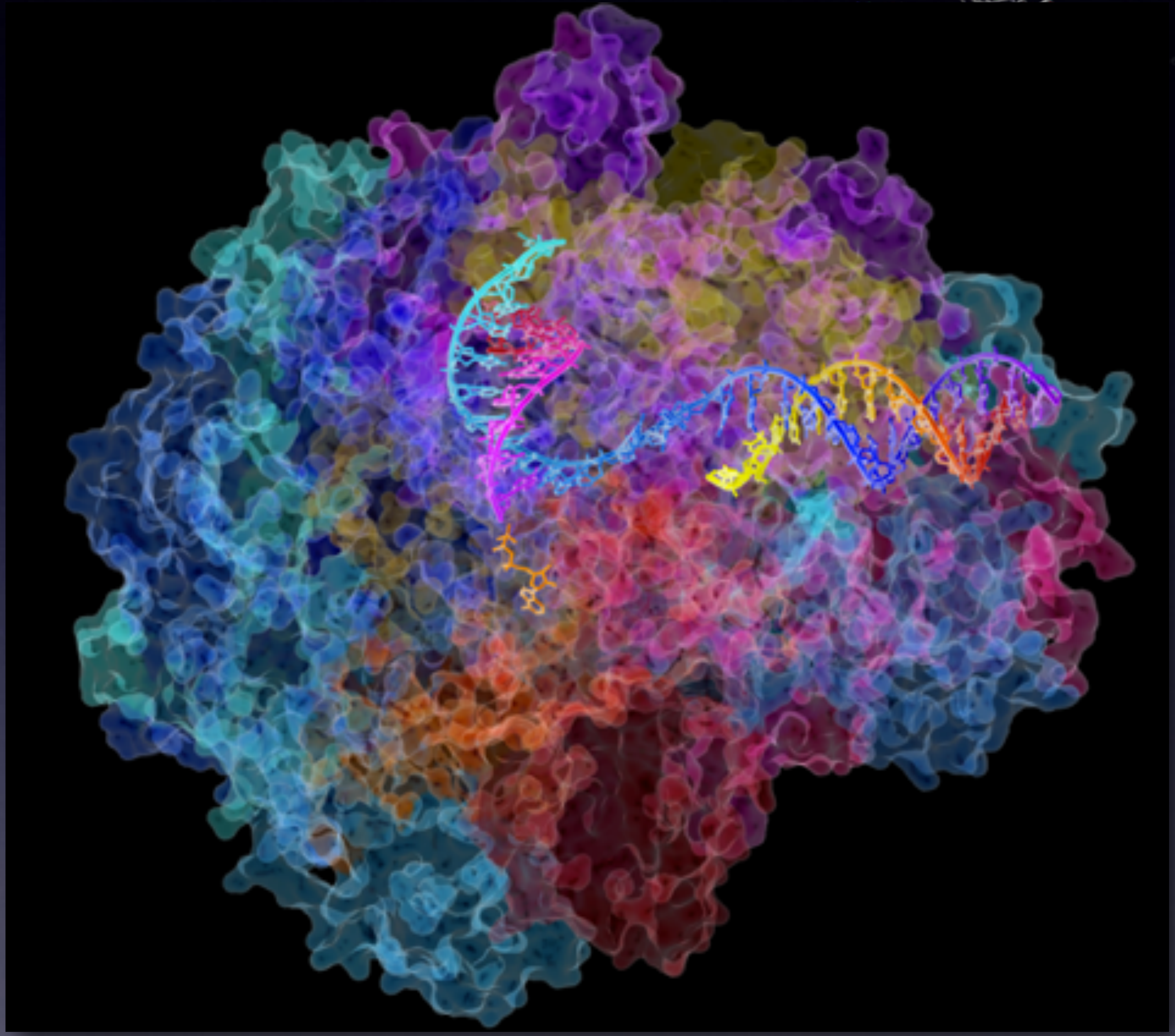
aquaporin

Protein structure



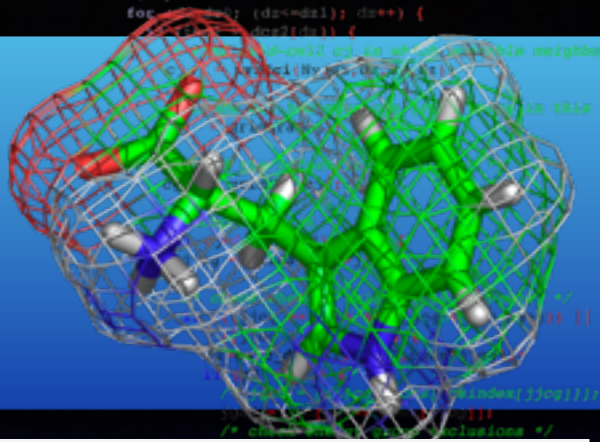
RNA Polymerase



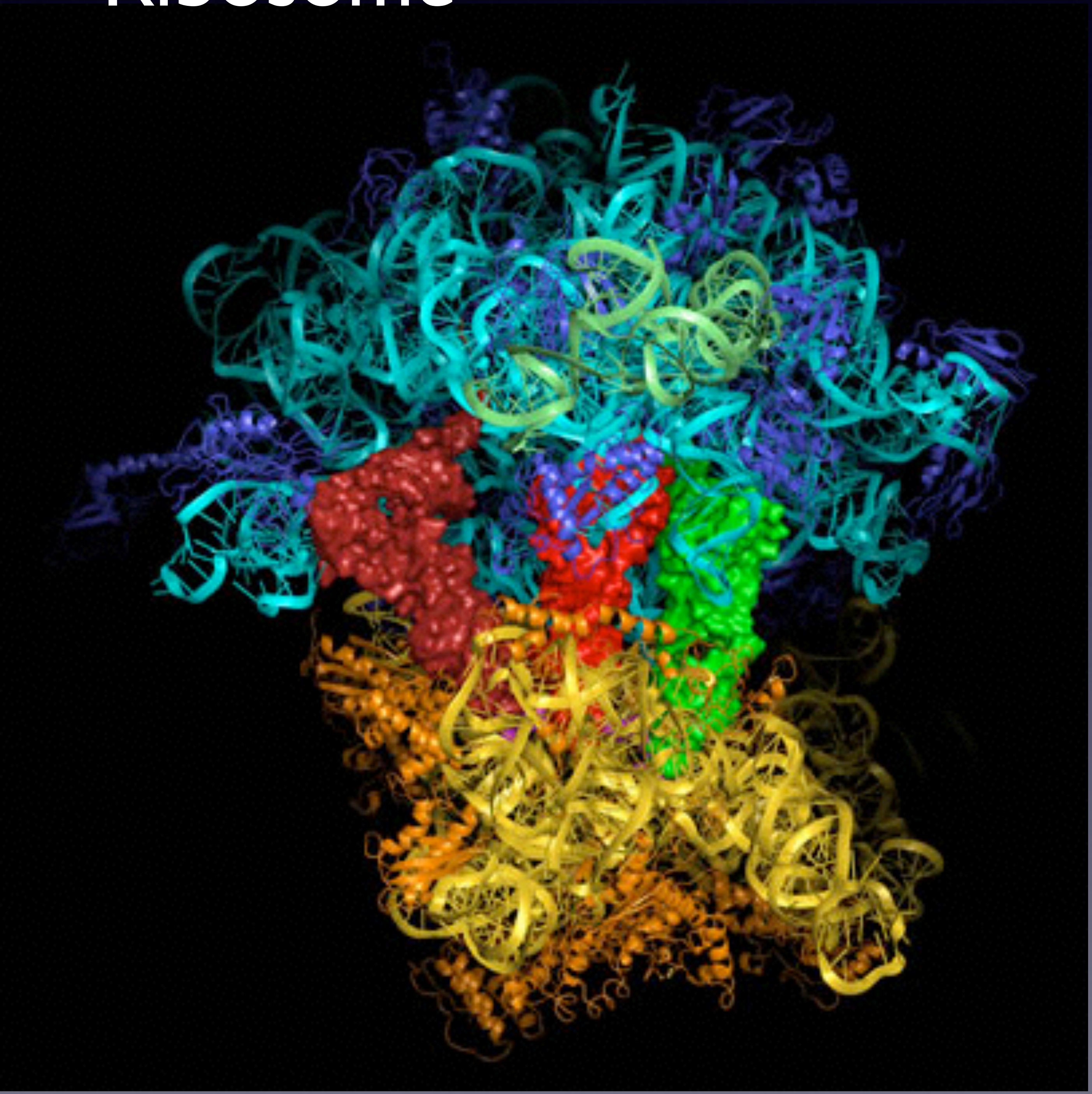


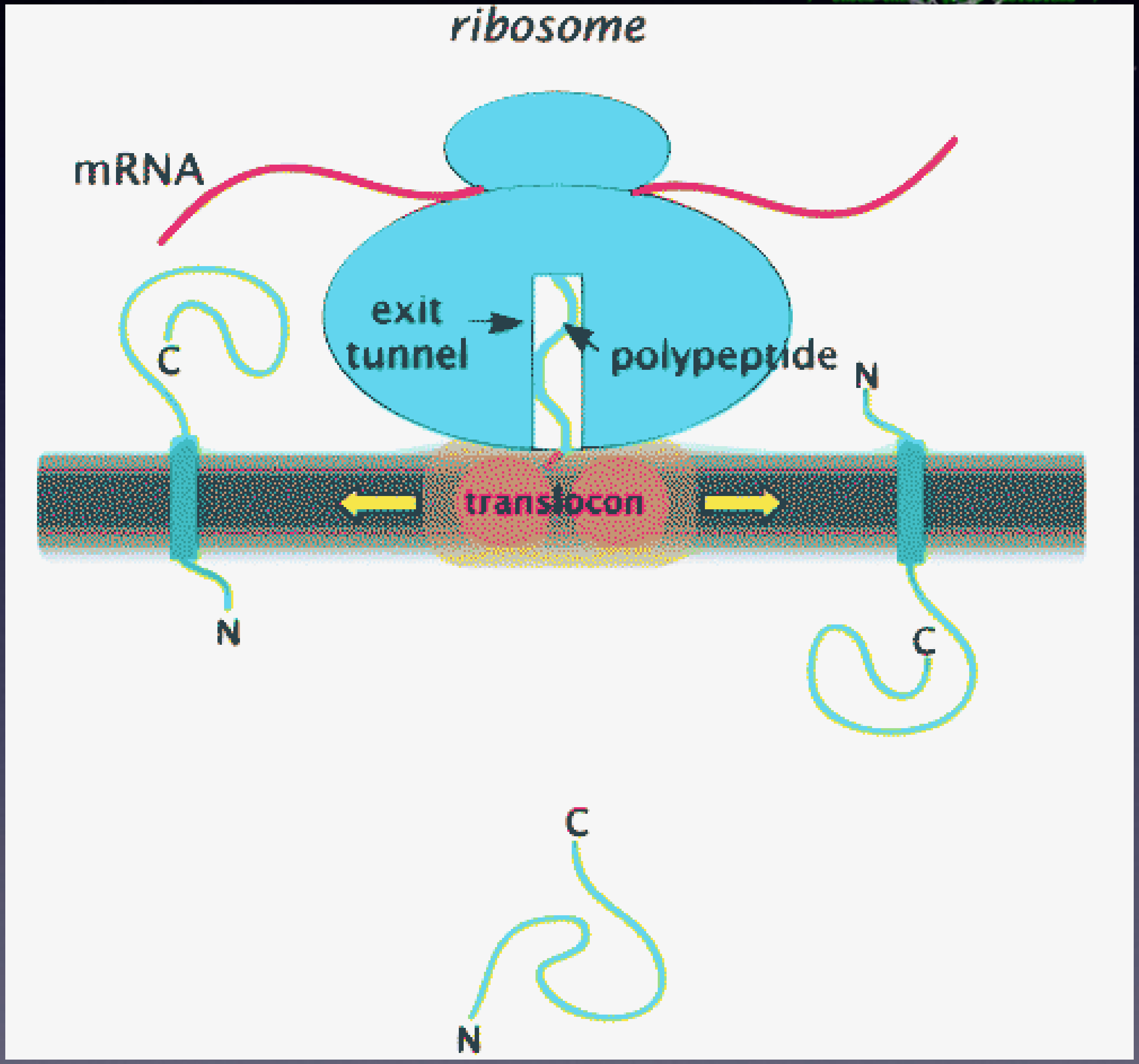
Roger Kornberg 2006

Protein structure



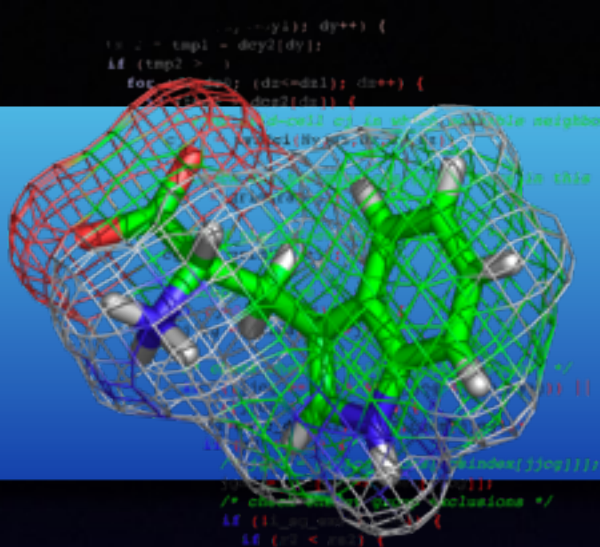
Ribosome



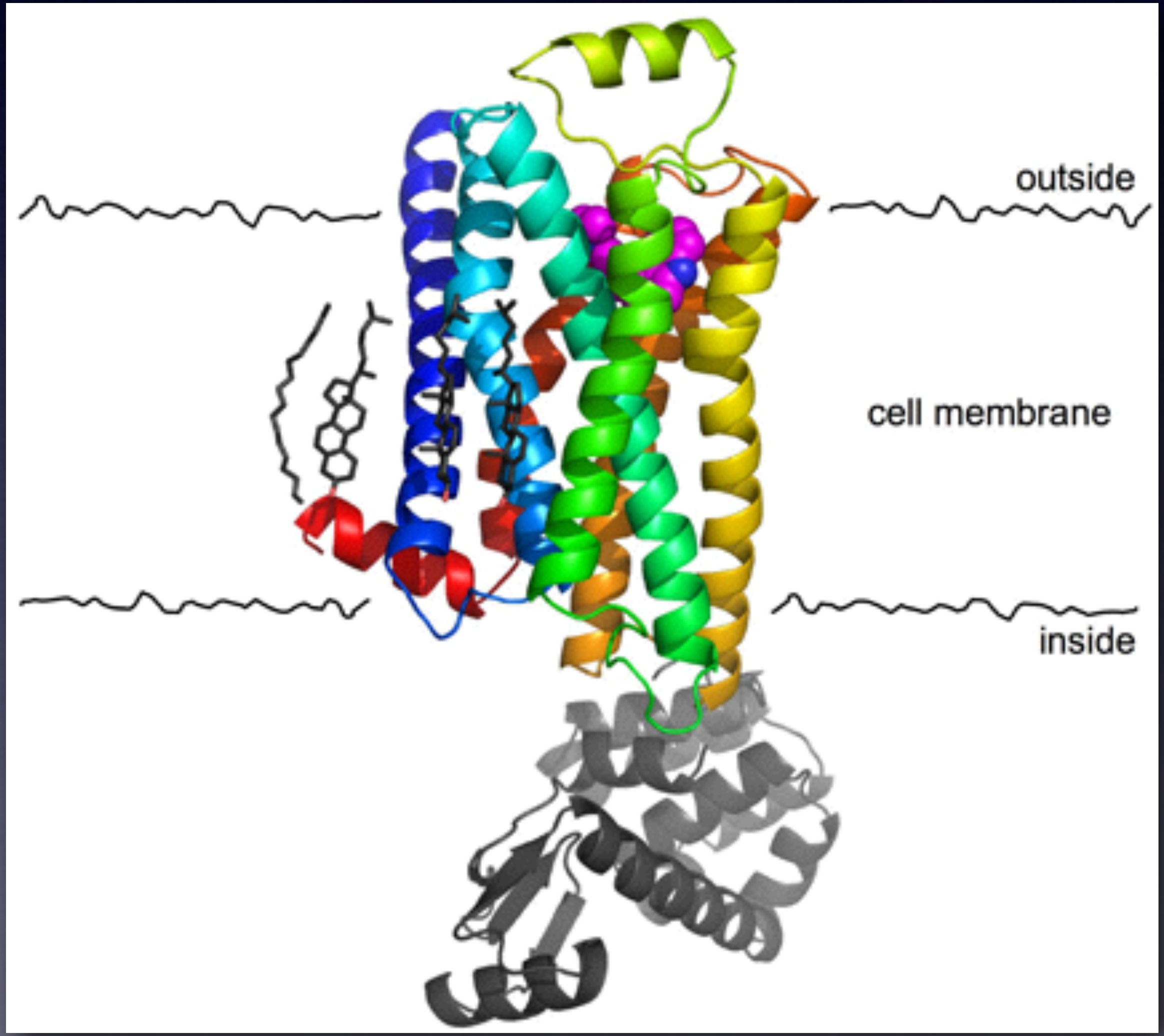


Tom Steitz & Peter Moore

Protein structure

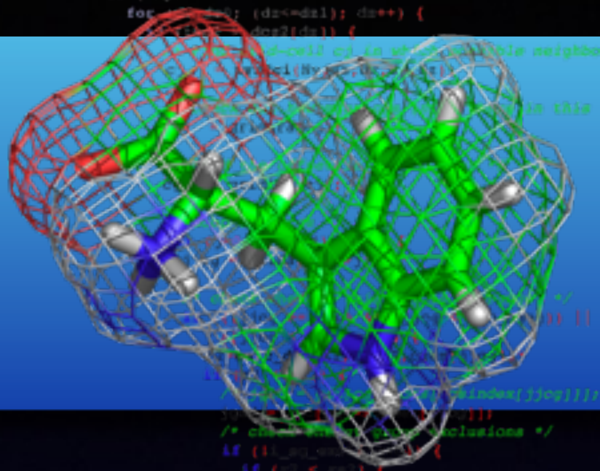


GPCRs



Brian Kobilka 2012

25 unique structures



Cryo-EM

THE REVOLUTION WILL NOT BE CRYSTALLIZED

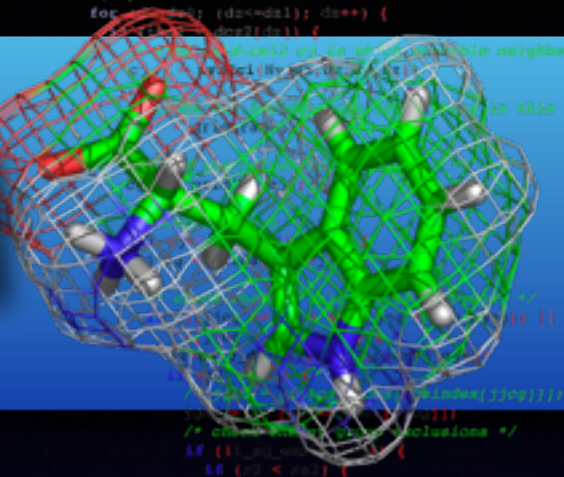
MOVE OVER X-RAY CRYSTALLOGRAPHY. CRYO-ELECTRON MICROSCOPY IS KICKING UP A STORM IN STRUCTURAL BIOLOGY BY REVEALING THE HIDDEN MACHINERY OF THE CELL.

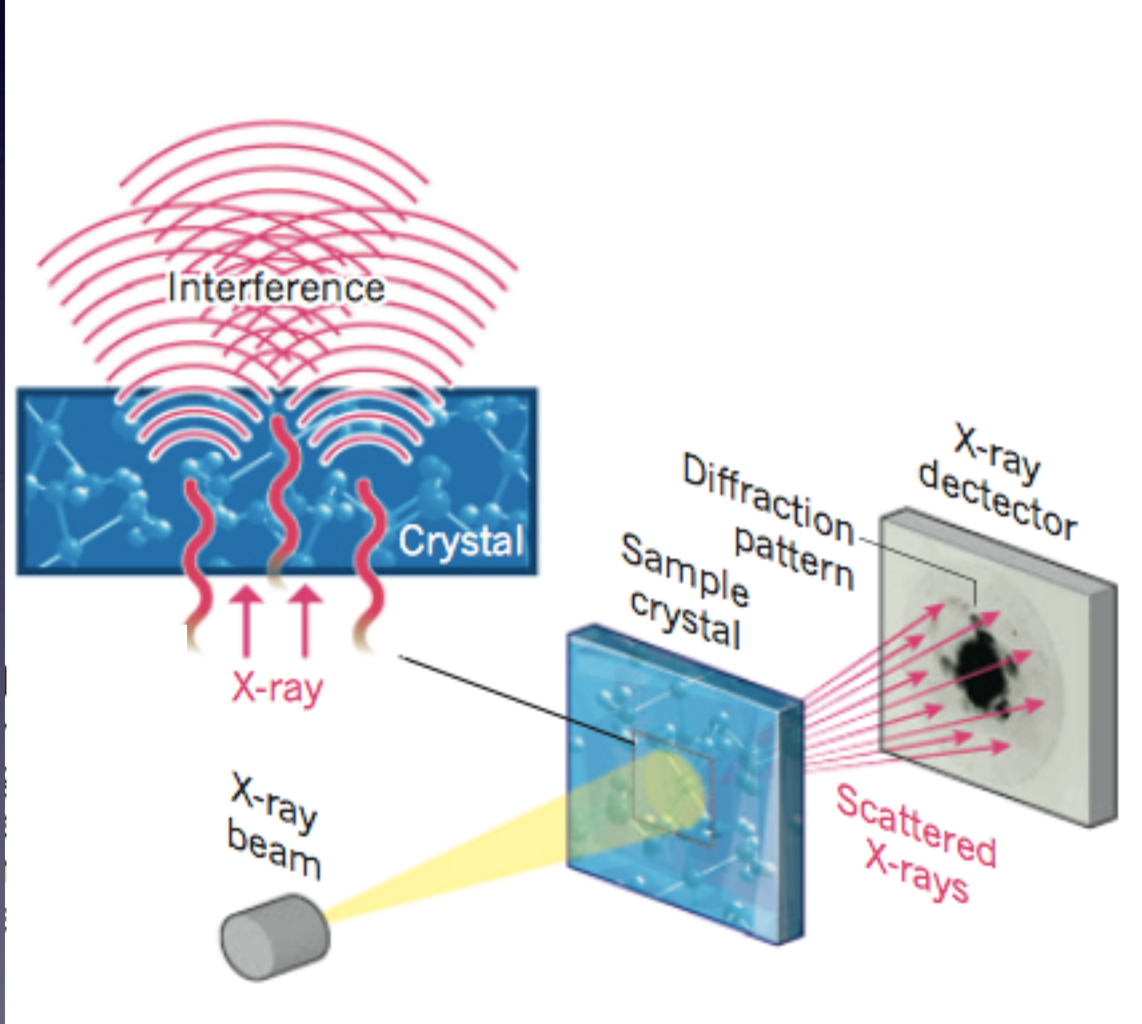
In a basement room, deep in the bowels of a steel-clad building in Cambridge, a major insurgency is under way.

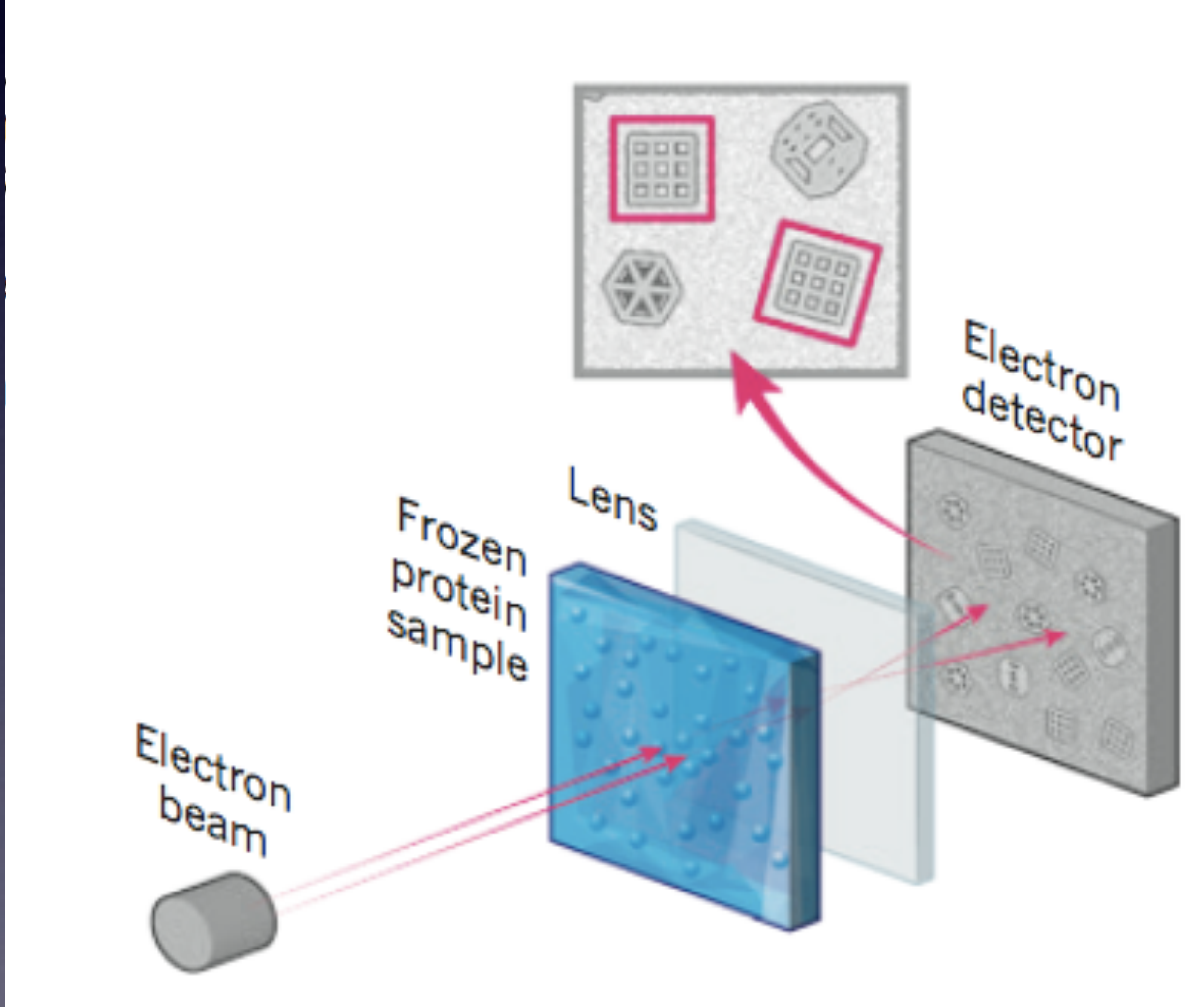
A hulking metal box, some three metres tall, is quietly beaming terabytes' worth of data through thick orange cables that disappear off through the ceiling. It is one of the world's most advanced cryo-electron microscopes: a device that uses electron beams to photograph frozen biological molecules and lay bare their molecular shapes. The microscope is so sensitive that a shout can ruin an experiment, says Sjors Scheres, a structural biologist at the UK Medical Research Council Laboratory of Molecular Biology (LMB), as he stands dwarfed beside the £5-million (US$7.7-million) piece of equipment. "The UK needs many more of these, because there's going to be a boom," he predicts.

Nature, 2015

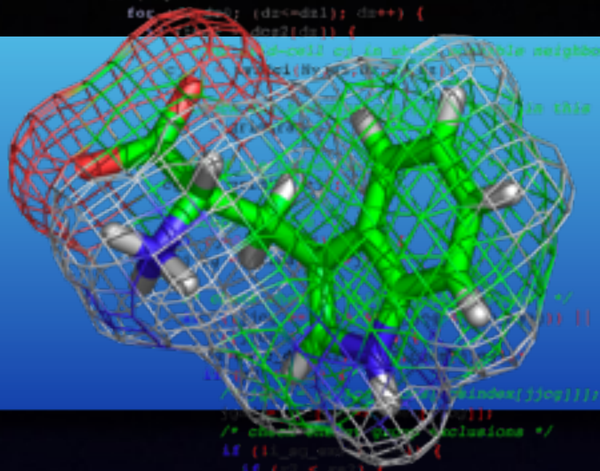
X-ray vs Cryo-EM

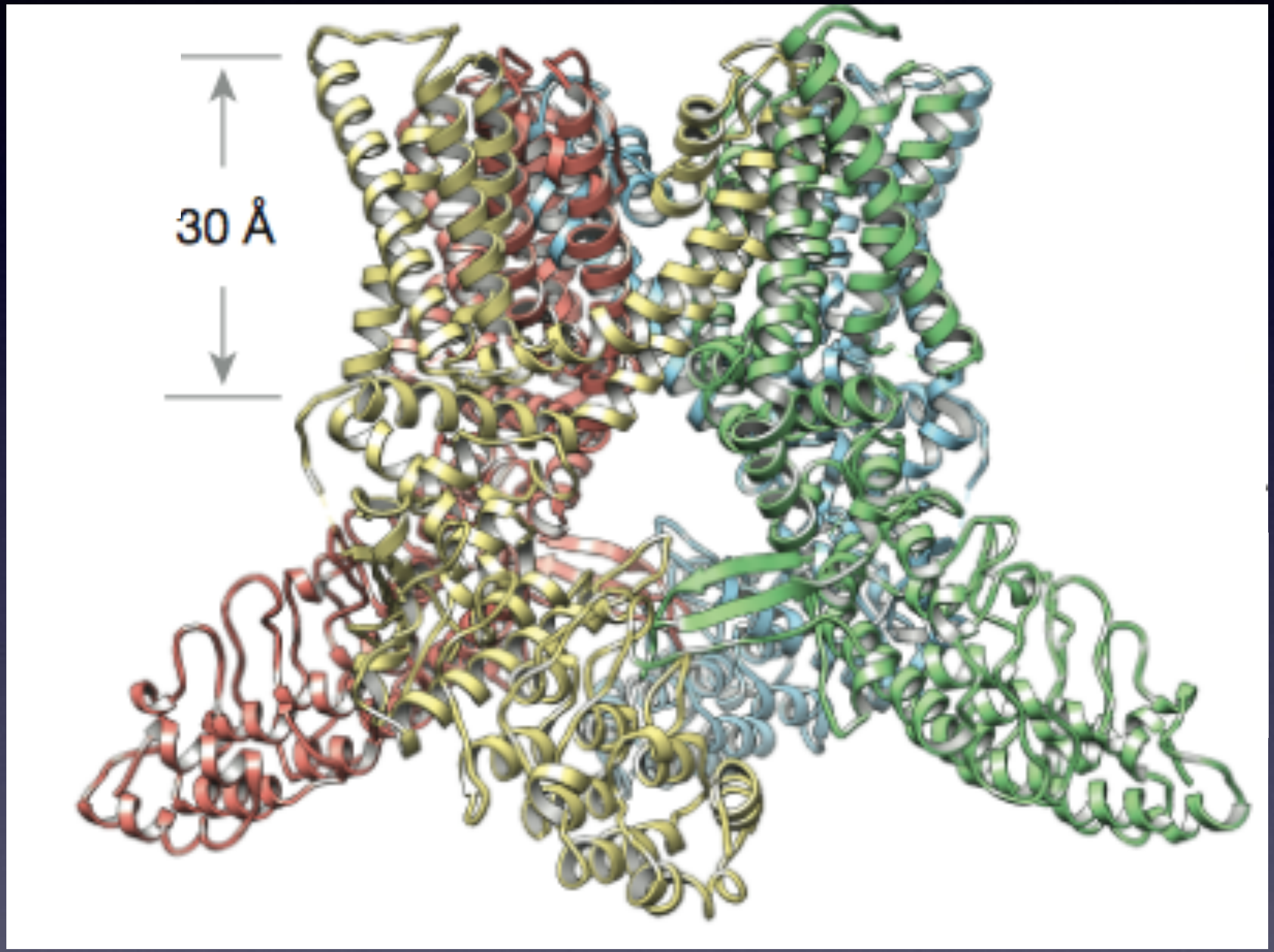


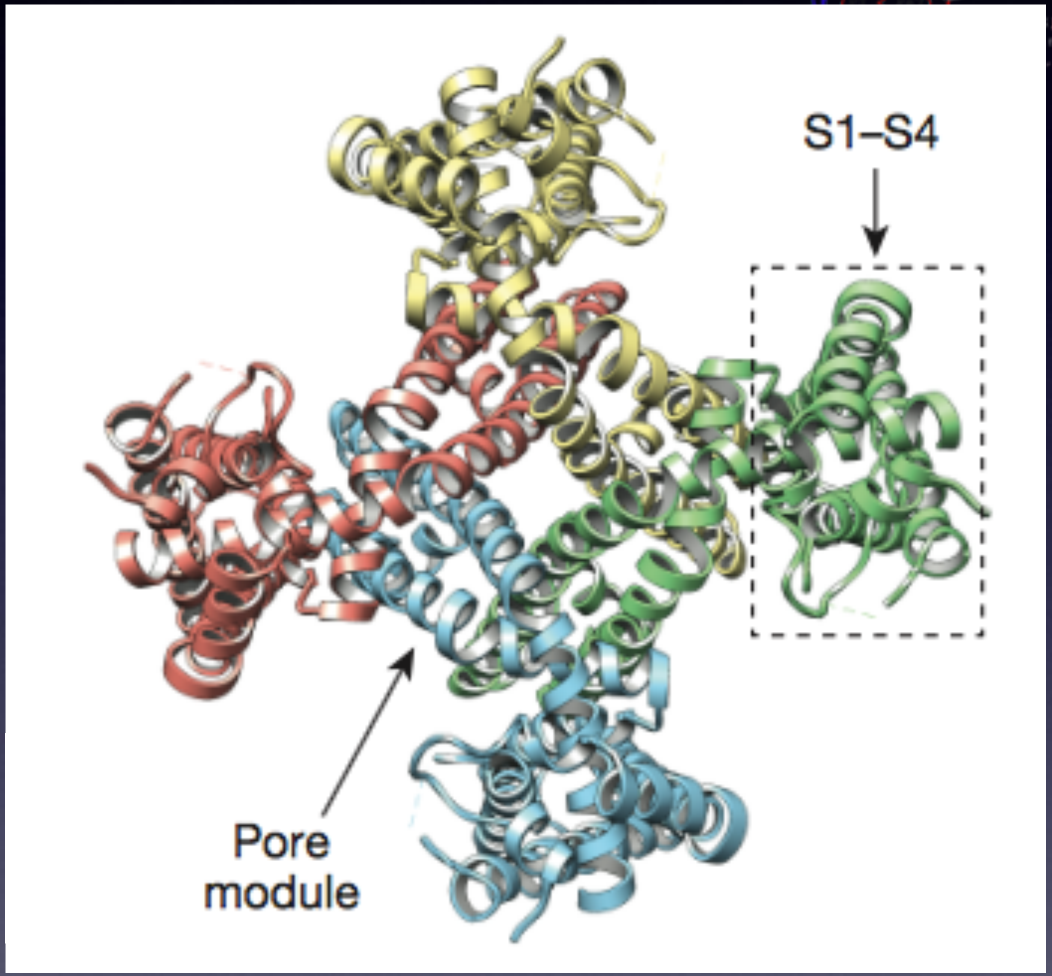


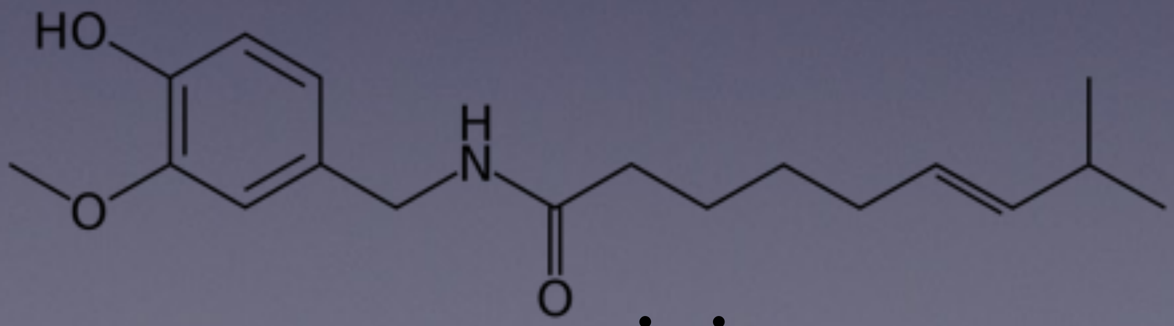


TRPV1

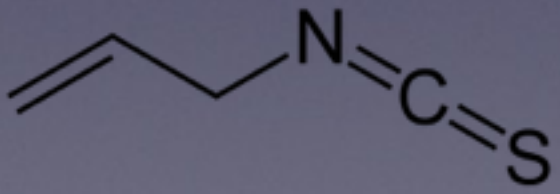






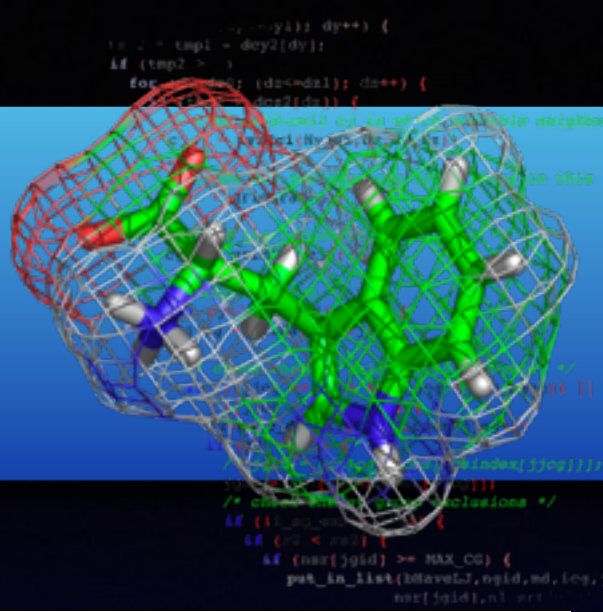


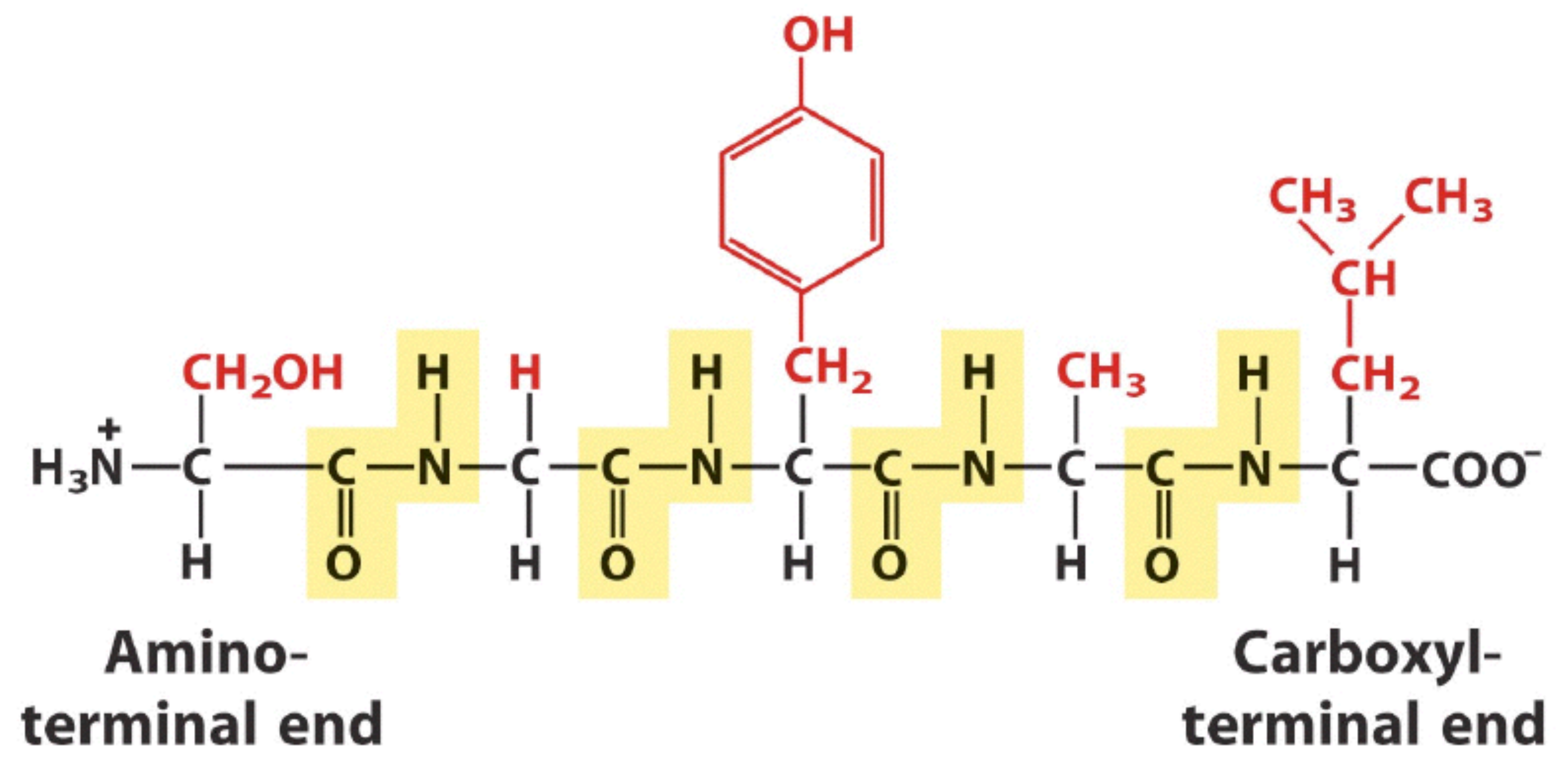
capsaicin



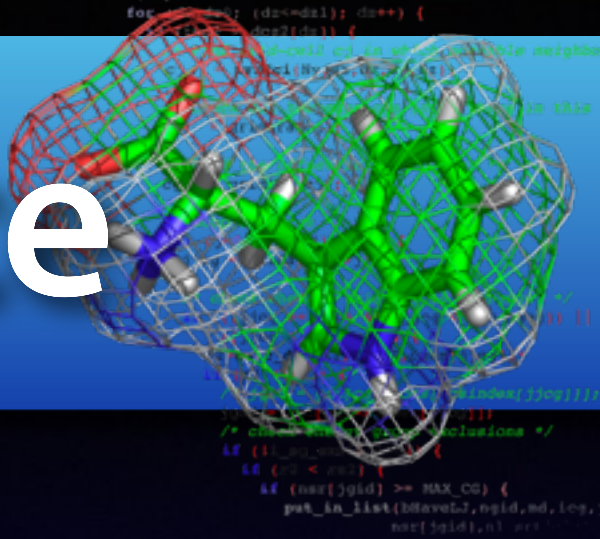
allyl isothiocyanate

Why this diversity?



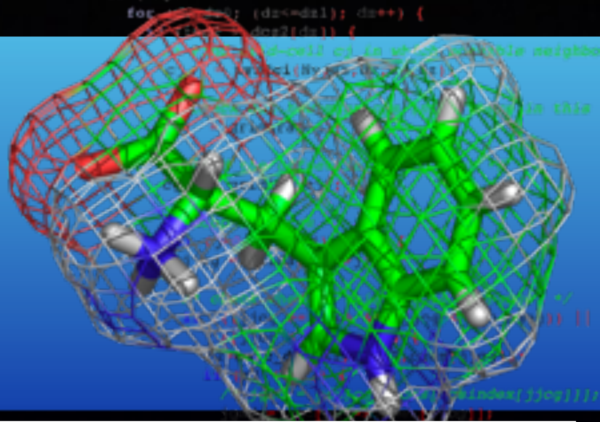


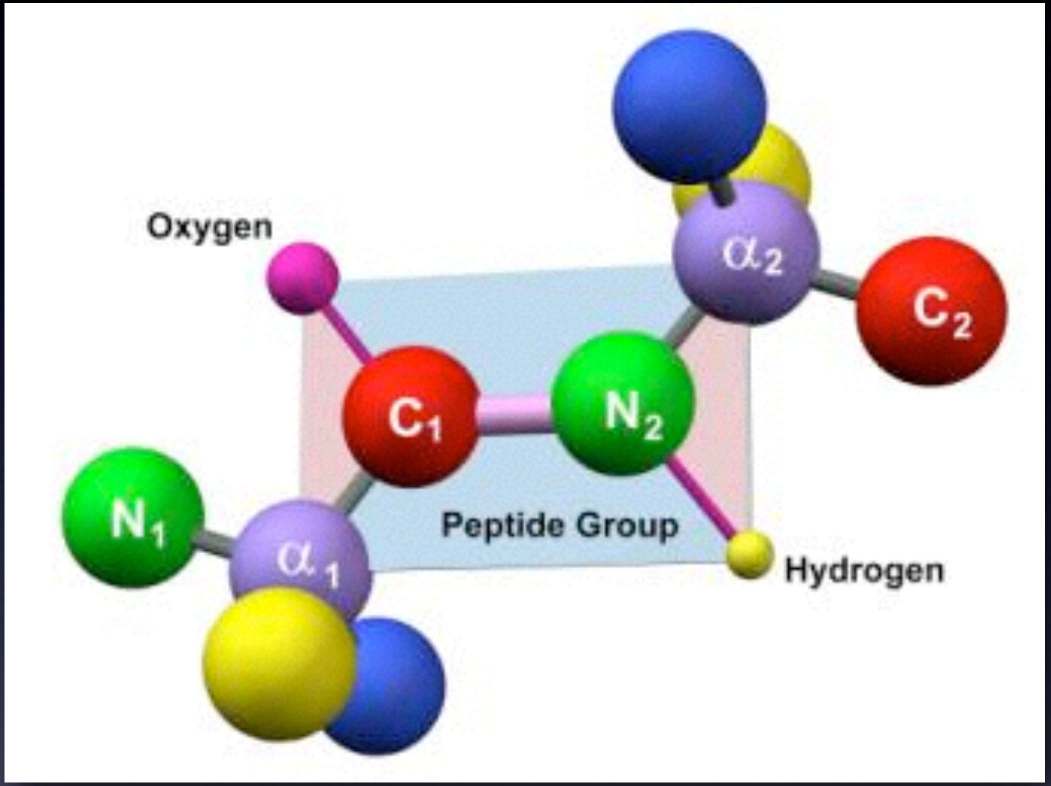
Conformational space

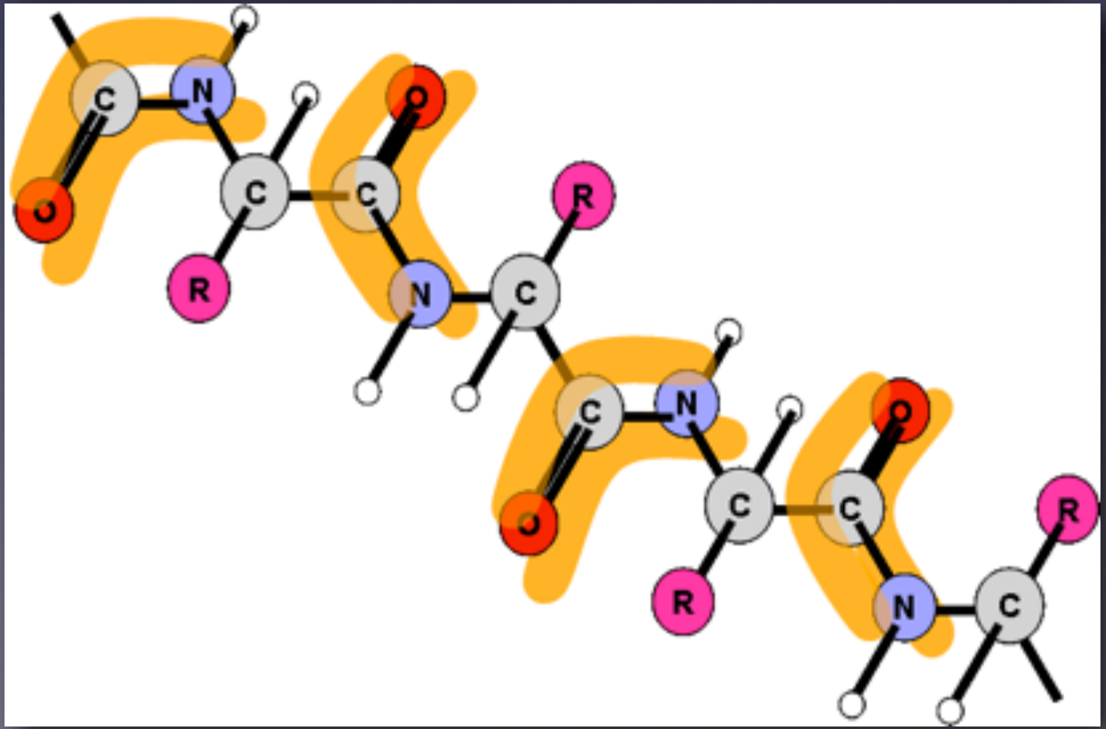


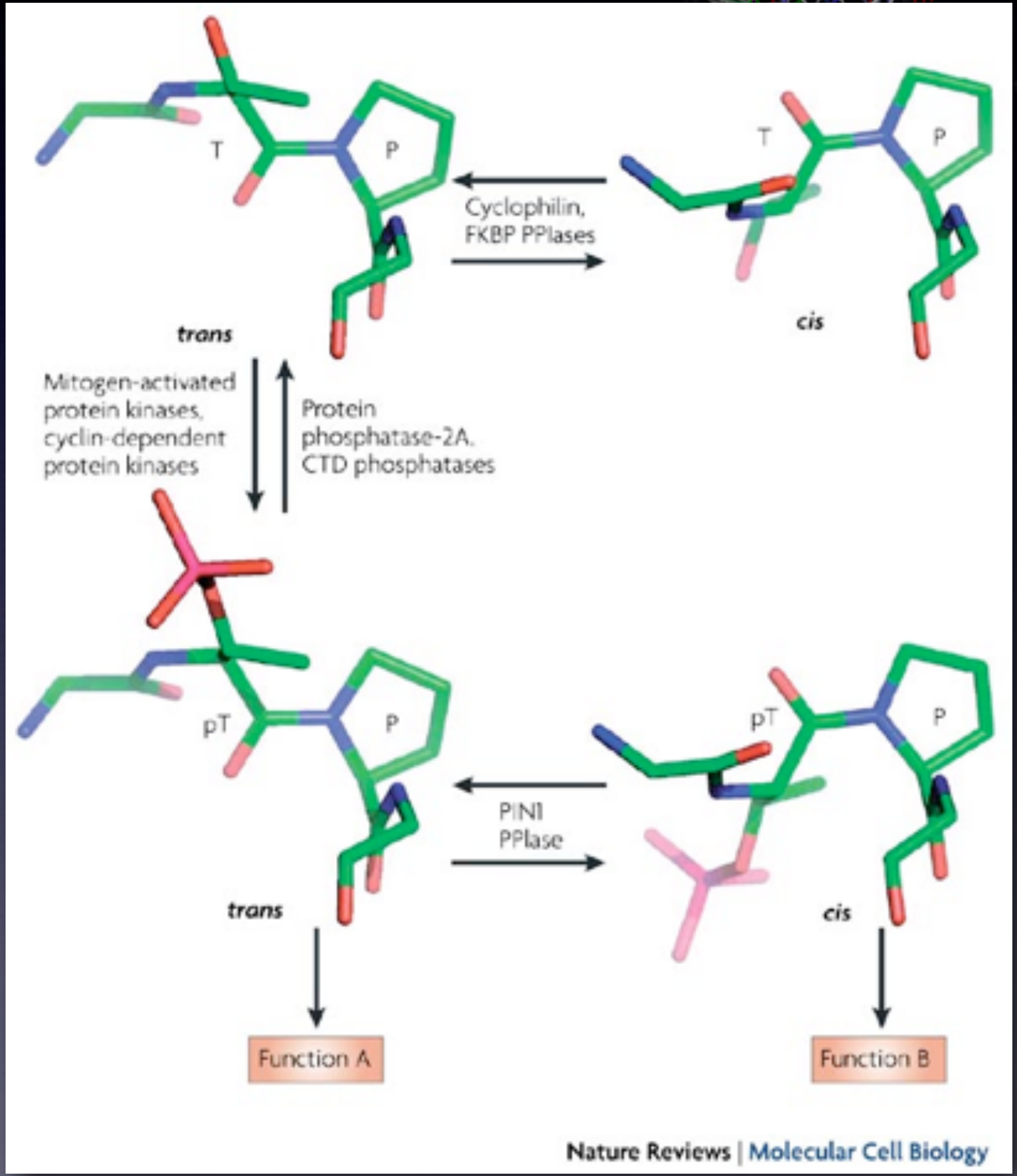
- How many conformations are there?
- Sample Φ,Ψ torsion in 10 degree units
  - 36 ‘states’ for each torsion
  - 36^2 states per residue
- For a 100-residue chain we get:
  - $(36^2)^{100}=36^{200}\approx10^{308}$ states for the chain
- Only one is the native structure

Cis/trans isomers





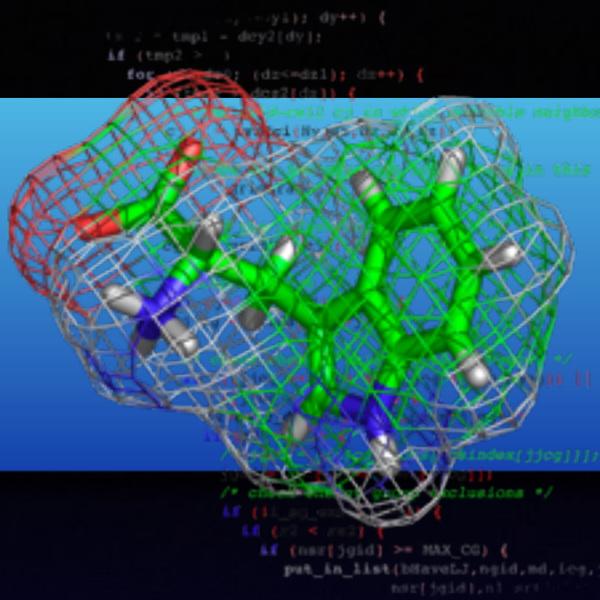




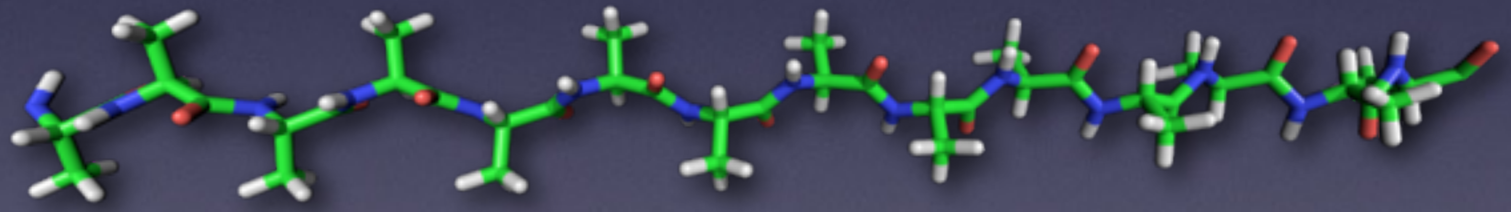
Nature Reviews | Molecular Cell Biology

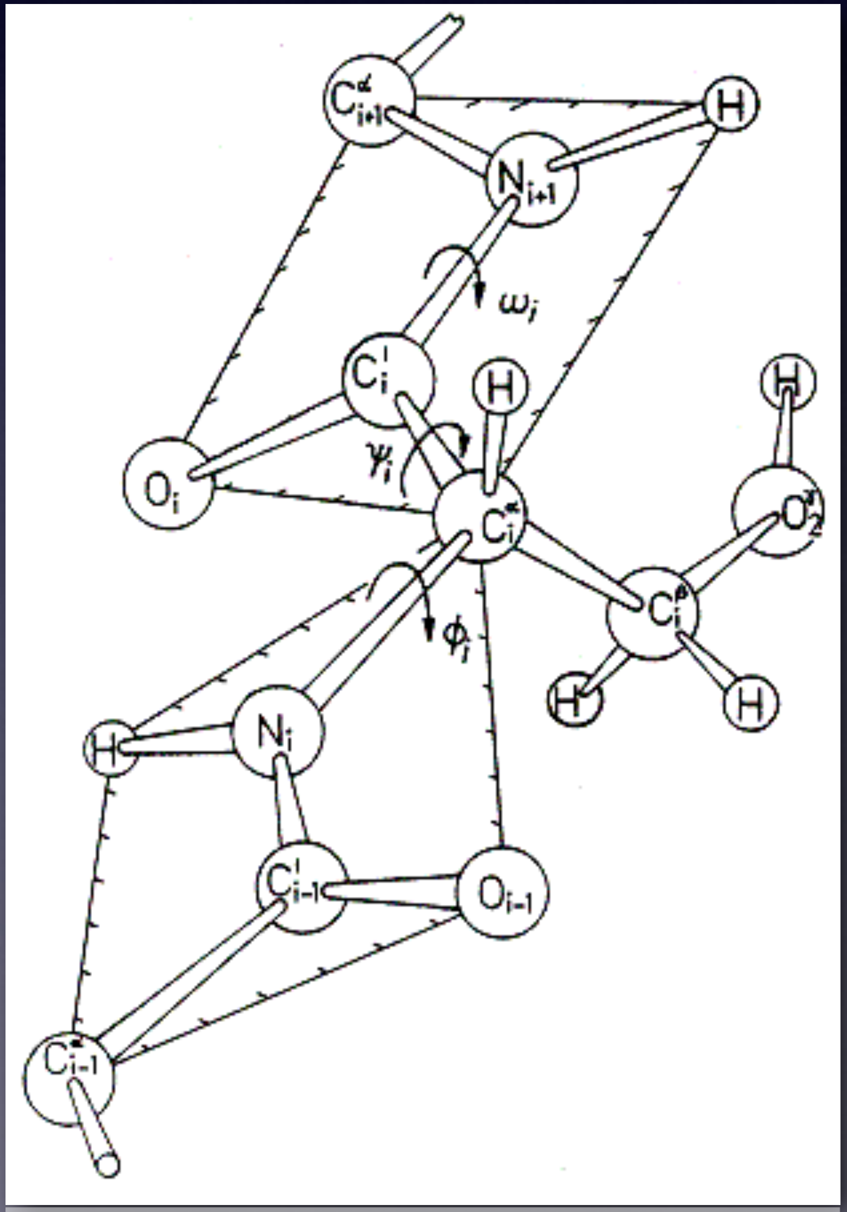
In Proline, both Cis & Trans occur, and it is important for function!

Discussion

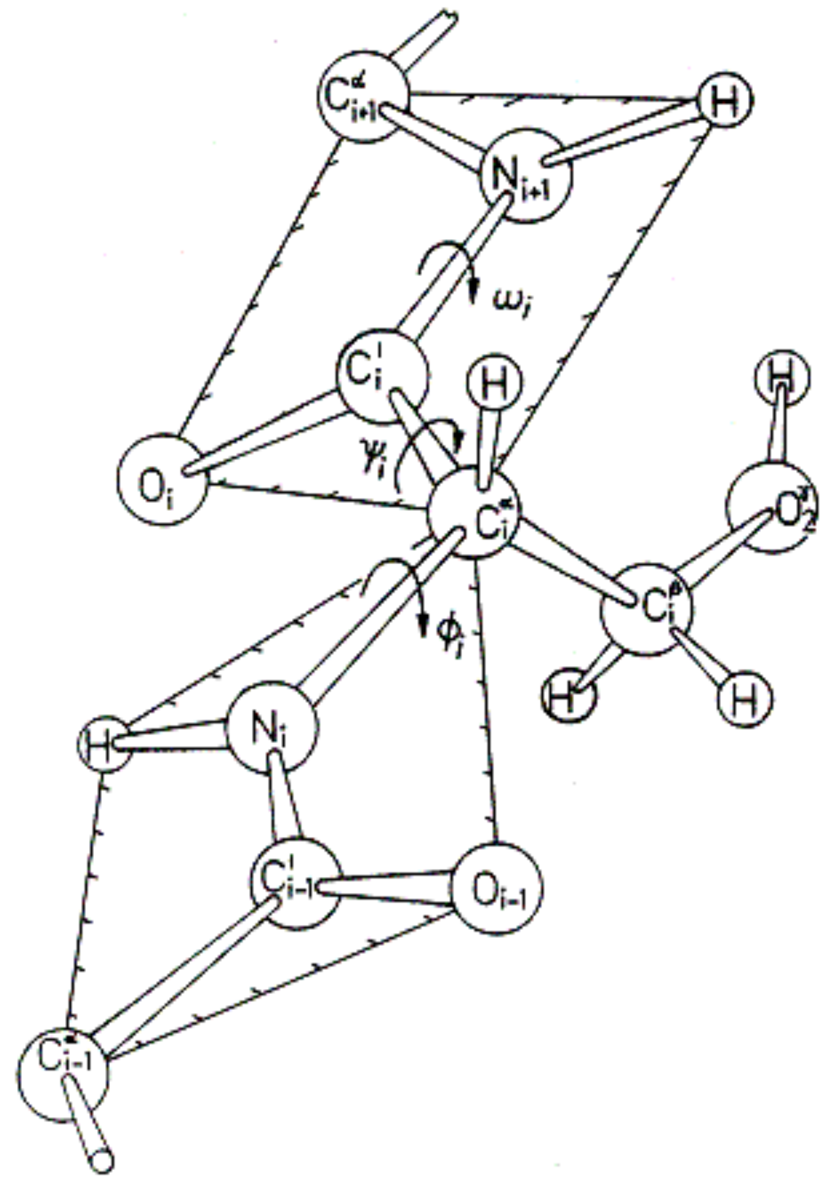


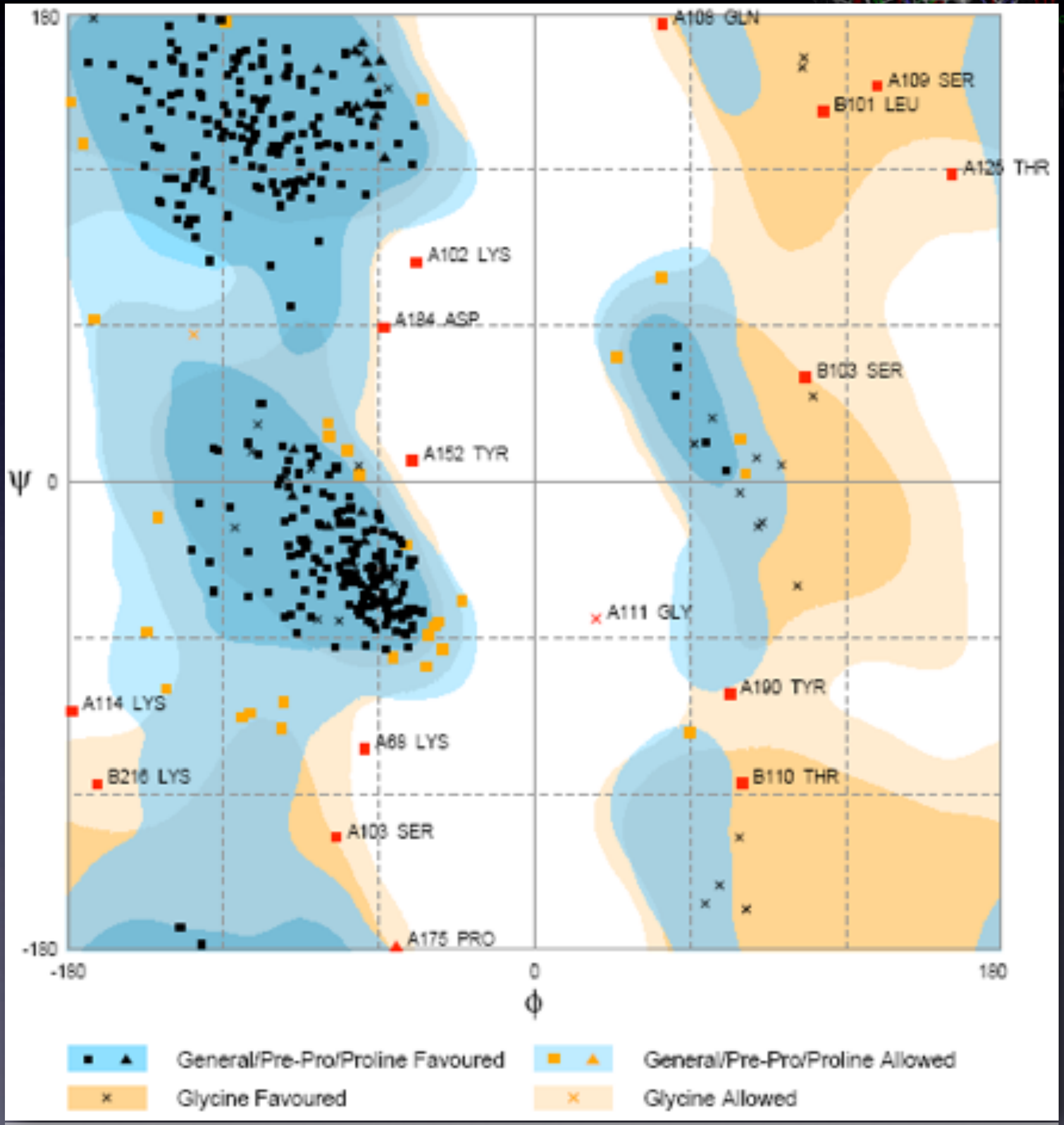
Which angle(s) affect protein structure the most?
and why?





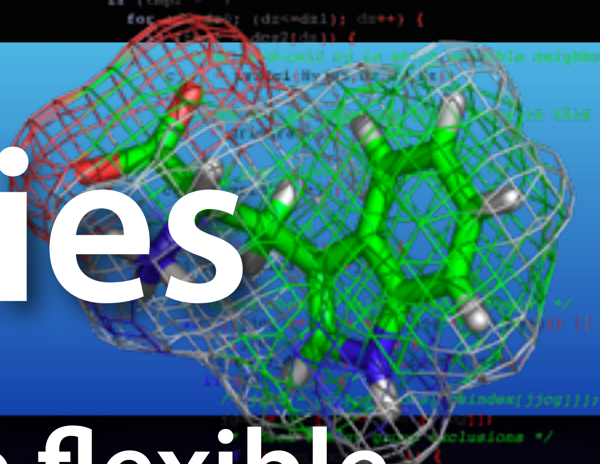
Ramachandran diagrams

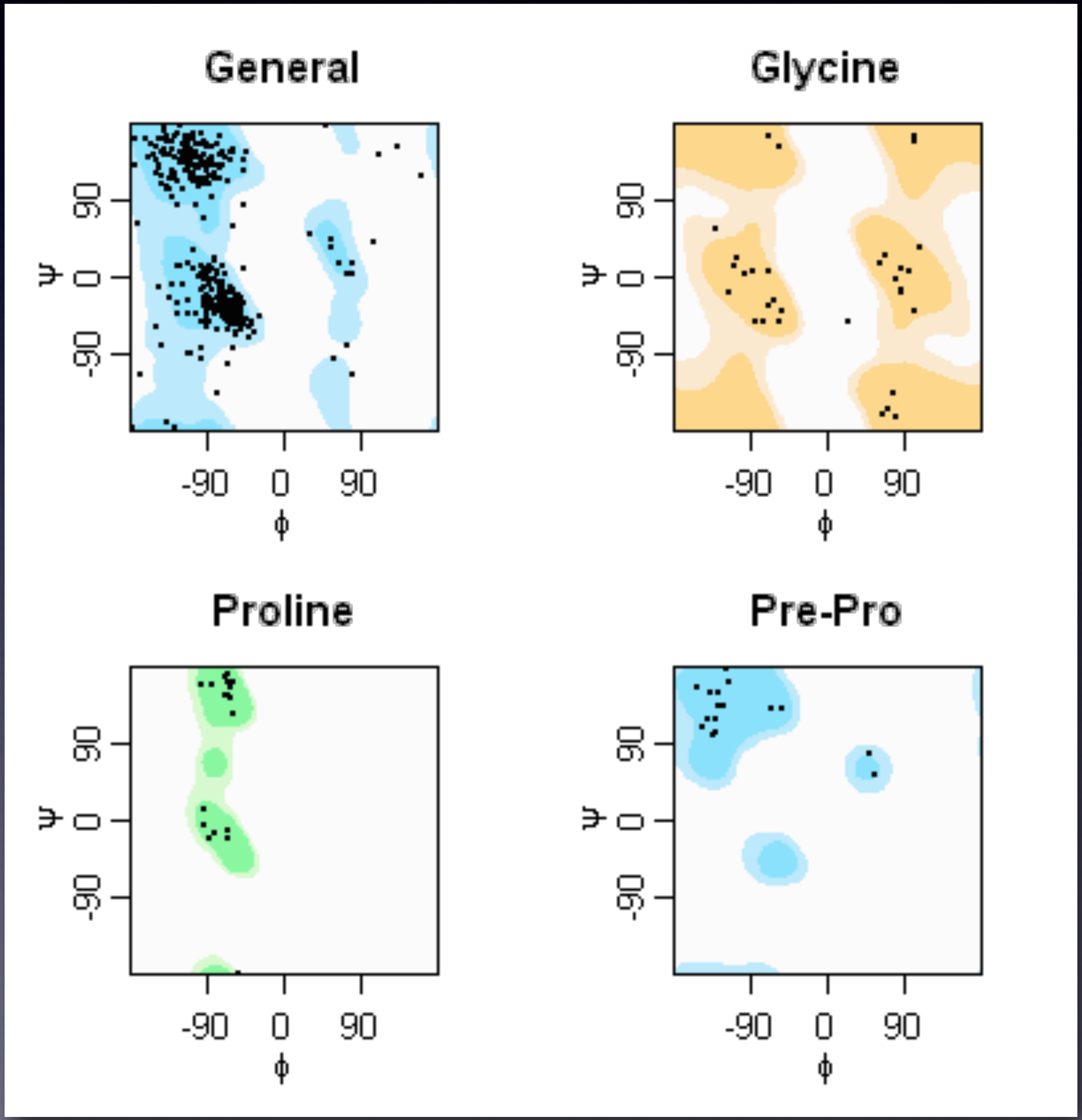




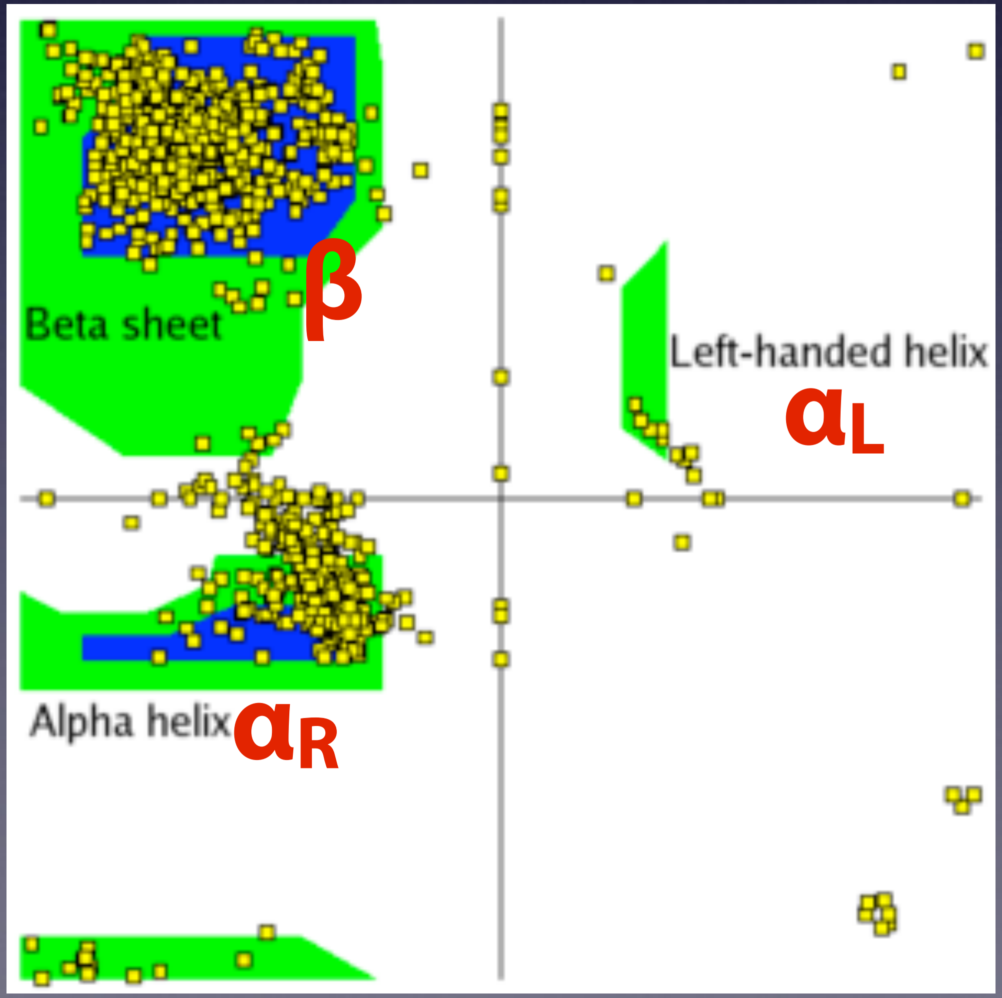
Natural degrees of freedom for amino acids
(due to steric clashes)

Ramachandran species

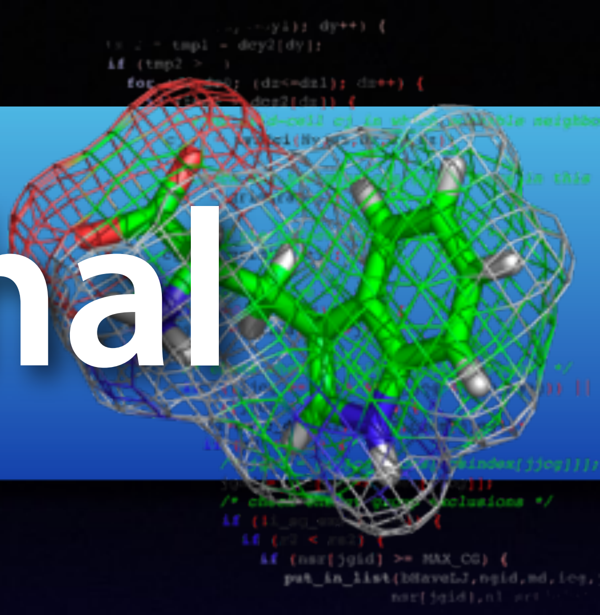




Glycine more flexible
Proline less flexible;
even messes up
previous residue!

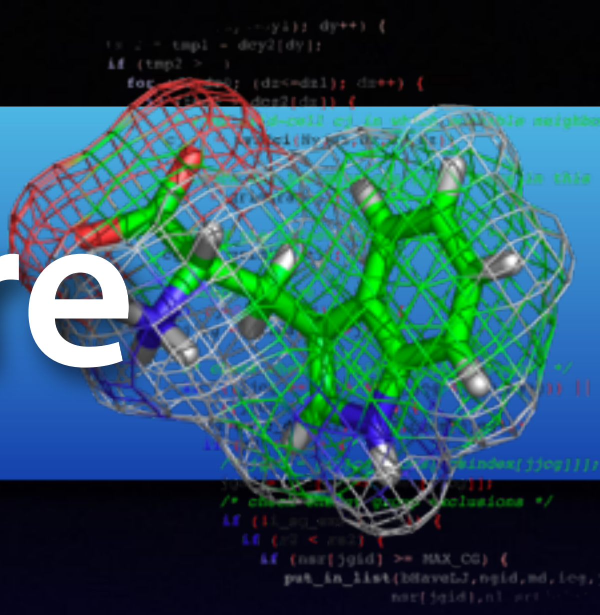


Anfinsen & Levinthal



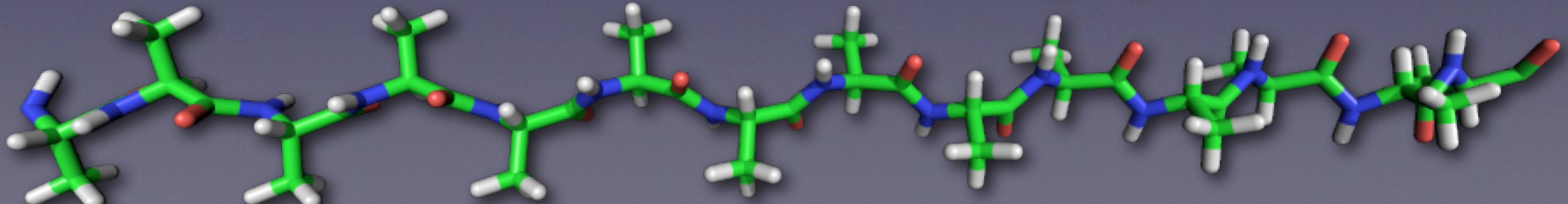
- Anfinsen: Proteins adopt the structure corresponding to the global minimum in free energy
- Levinthal: But how can a protein find that? Even with just 2 states per amino acid and 100 residues there are 2^100 states! (*Levinthal's Paradox*)

Polypeptide structure



- Backbone degrees of freedom:
  - Peptide (Ω) bond (trans)
  - Φ (C-N-CA-C),Ψ (N-CA-C-N) torsions
- Side chain degrees of freedom:
  - χ_1,χ_2,χ_3 torsions

Rotational barrier around
“single” (CH3-CH3) bond
is roughly 2-4 kcal/mol



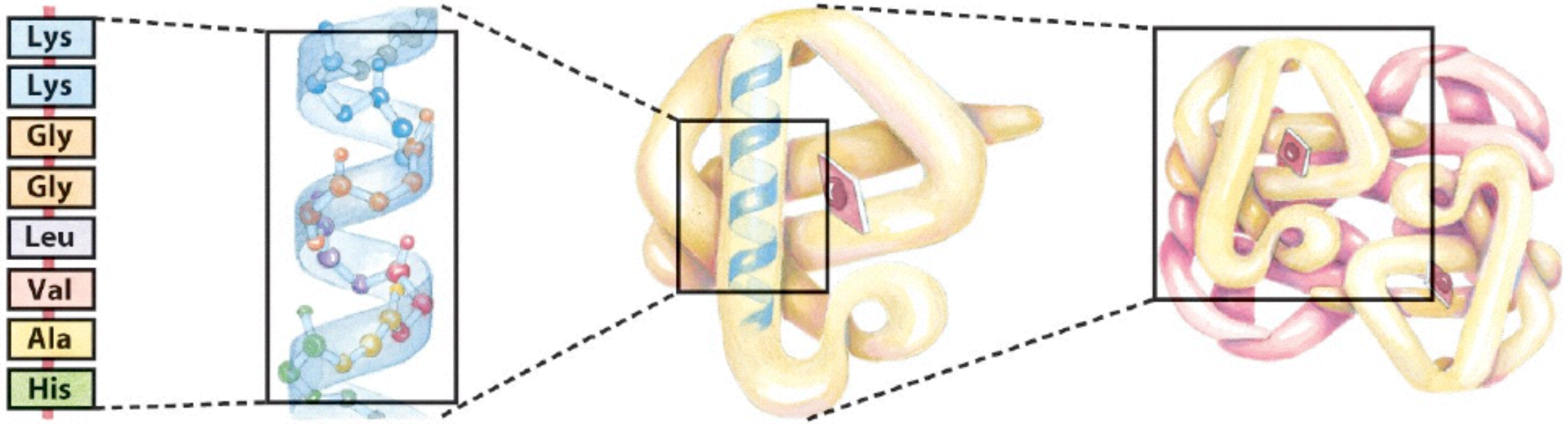
Protein Structure

Primary Structure

Secondary Structure

Tertiary Structure

Quaternary Structure



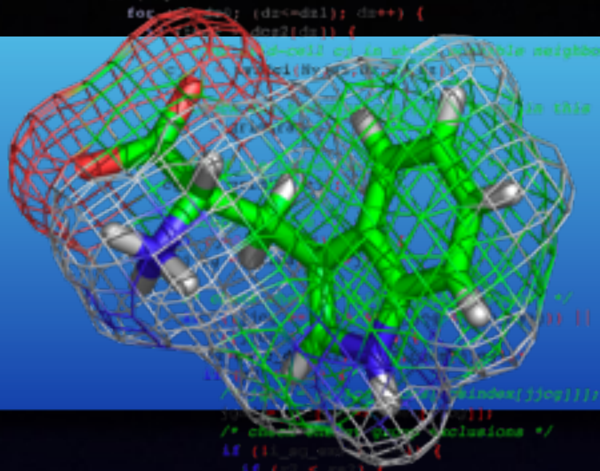
Residues

Helix

Chain

Subunits

Helices



- Naturally occuring amino acid helices are right-handed
- Nomenclature: N_M-helix
  - Residue i h-bonds to i+N
  - M atoms per helical turn
- 4_{13} (α) helix - most common!
- 3_{10} helix

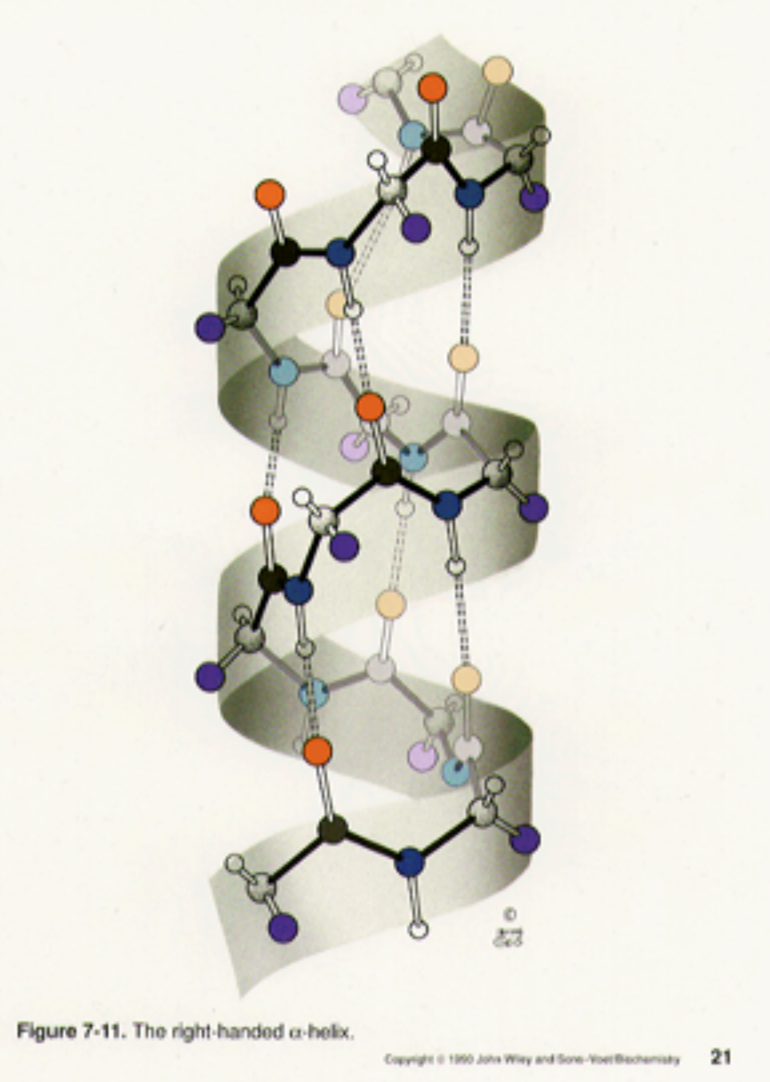
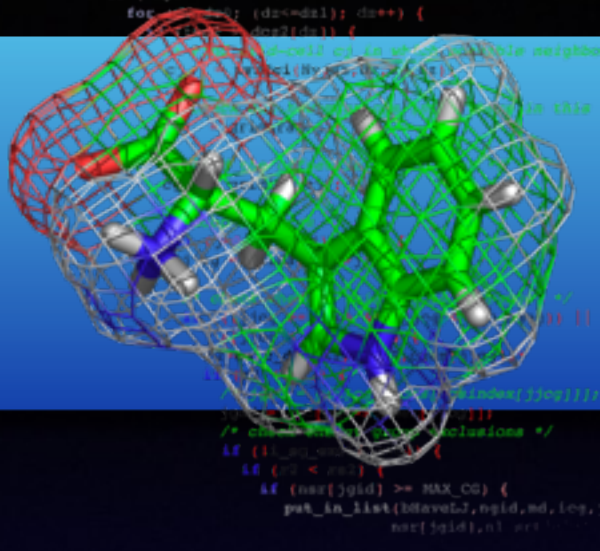
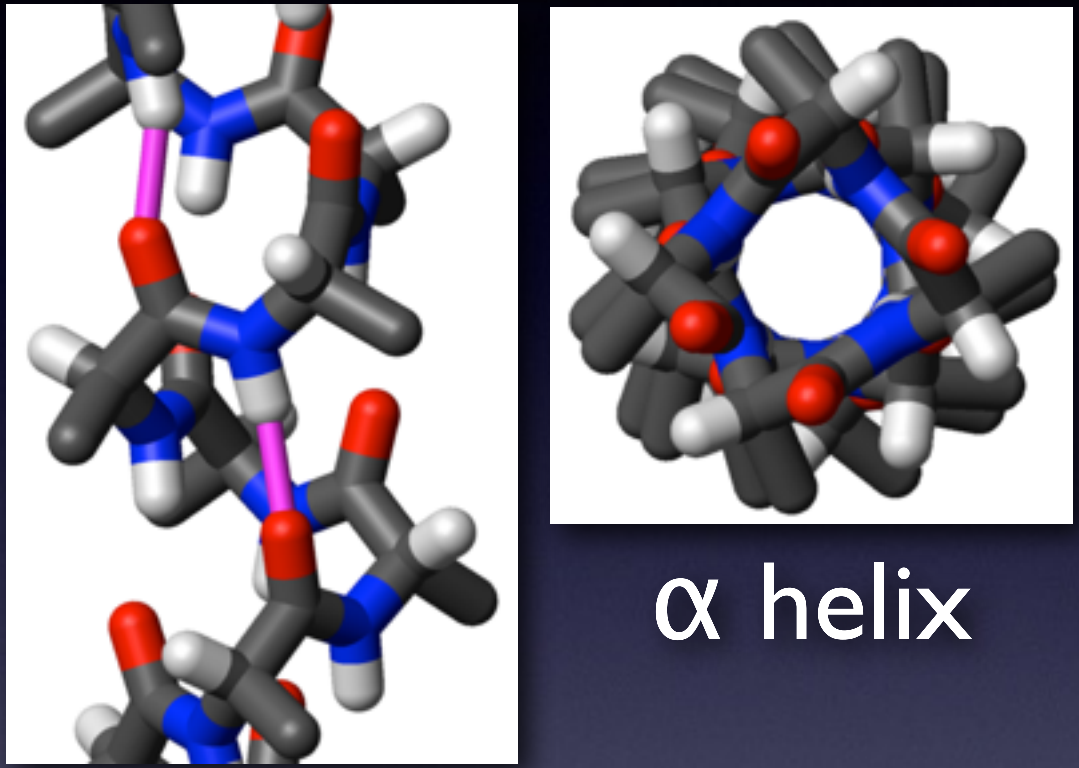


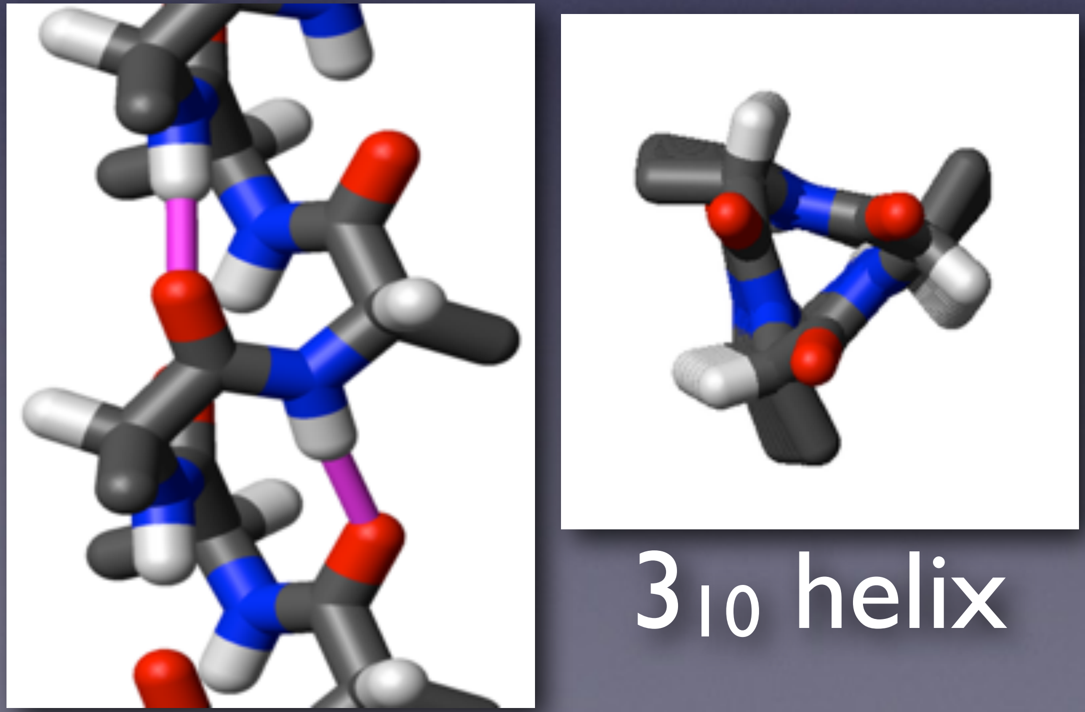
Figure 7-11. The right-handed α-helix.



Helix examples

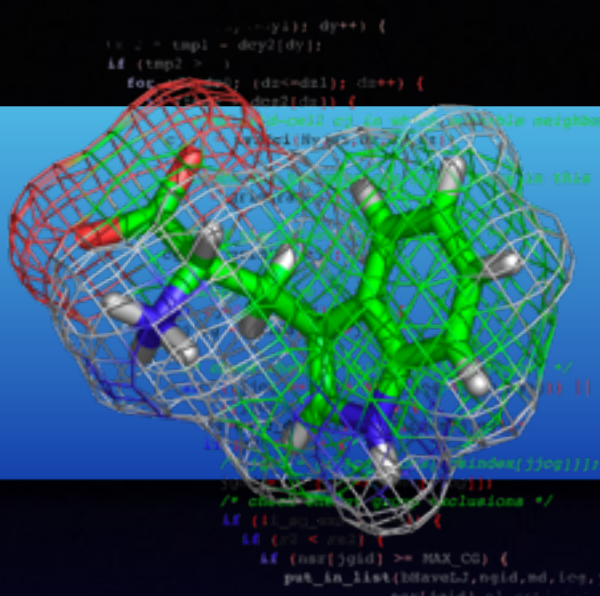


α helix



3_{10} helix

The α-helix is the most relaxed of the helical structures



Discussion

Which secondary structural element is more stable?

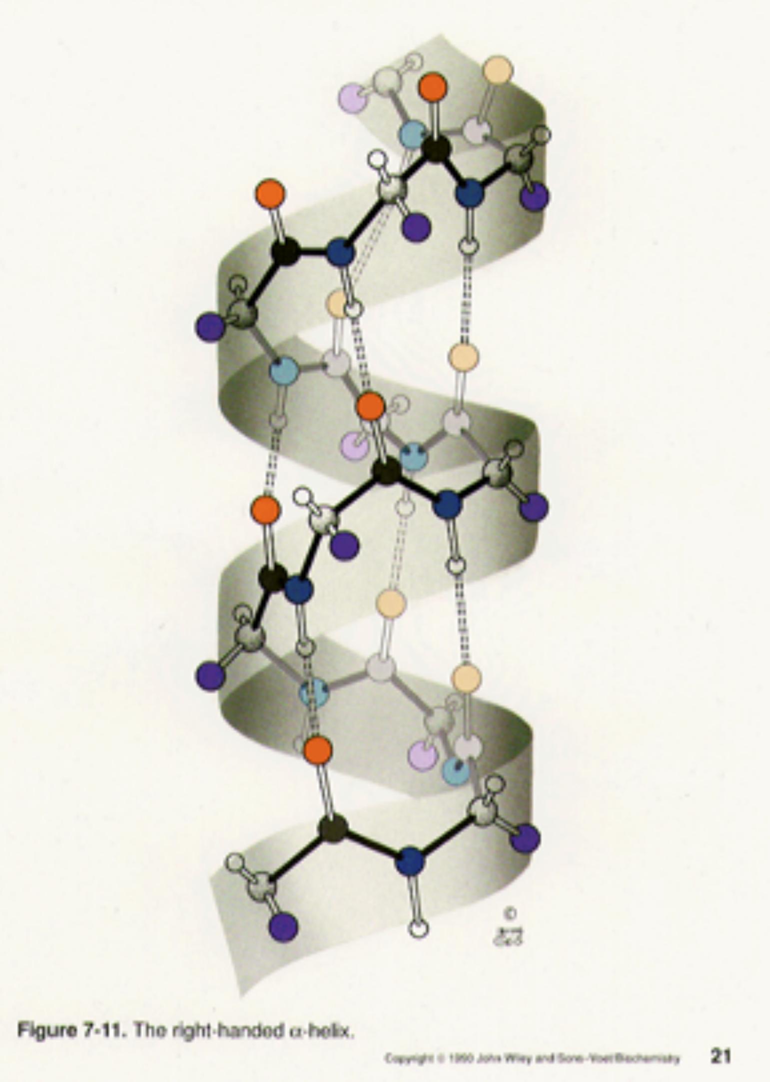


Figure 7-11. The right-handed α-helix.

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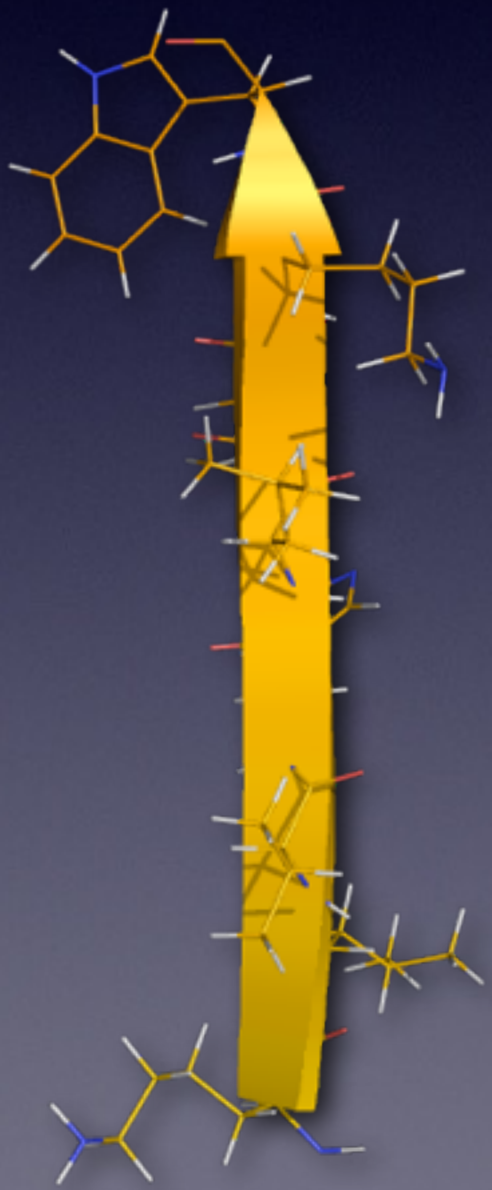
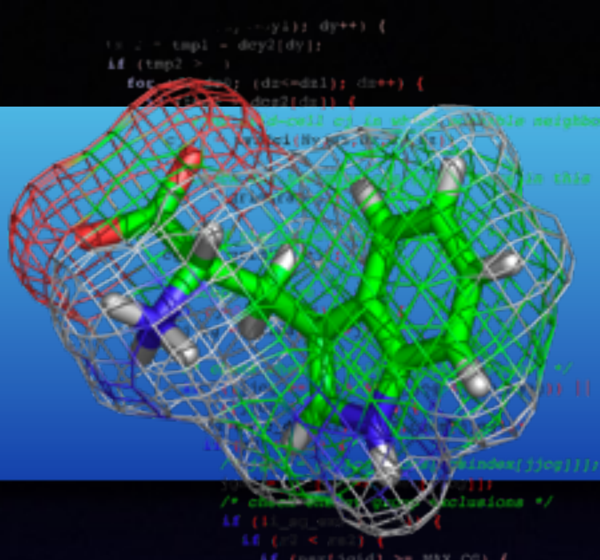
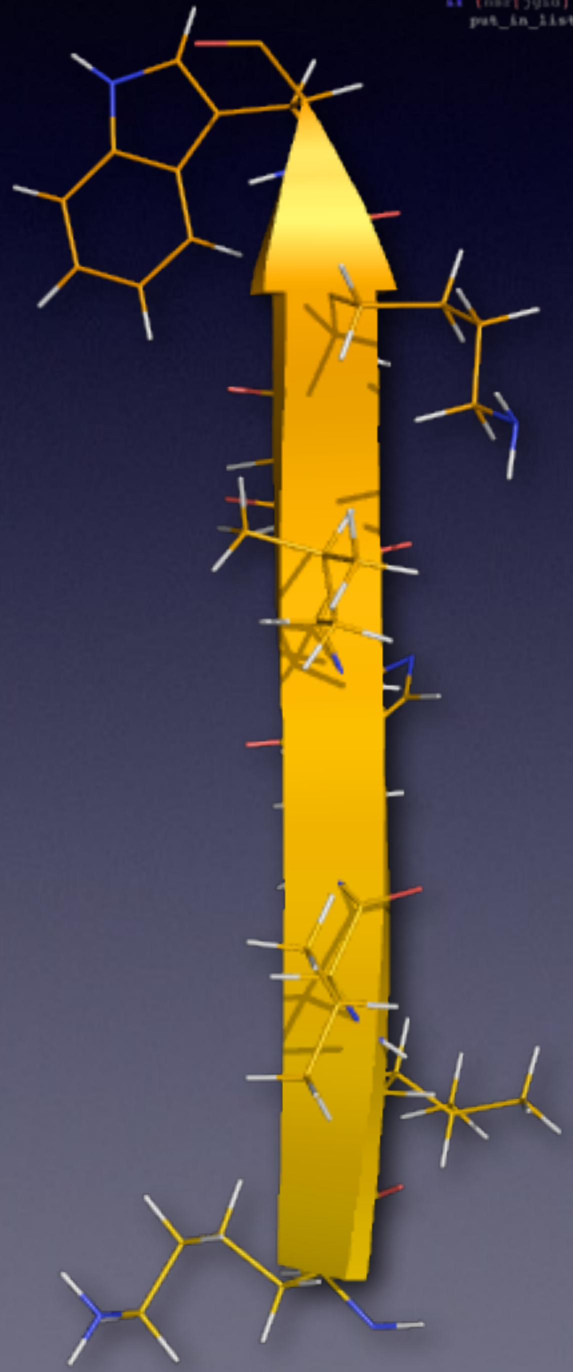


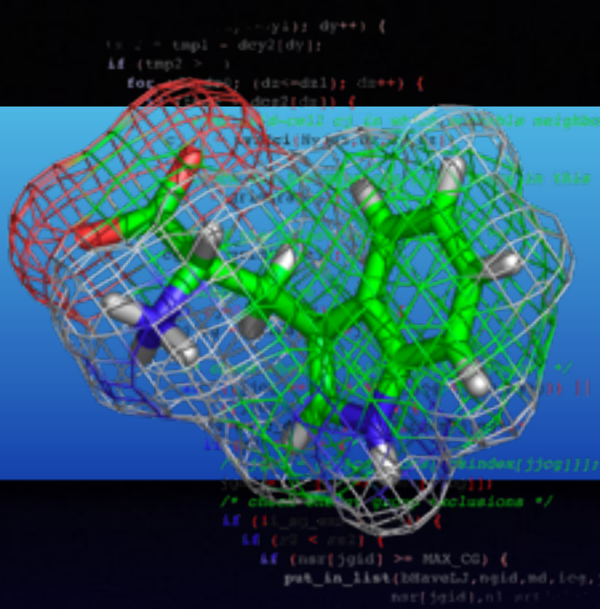
Secondary structure

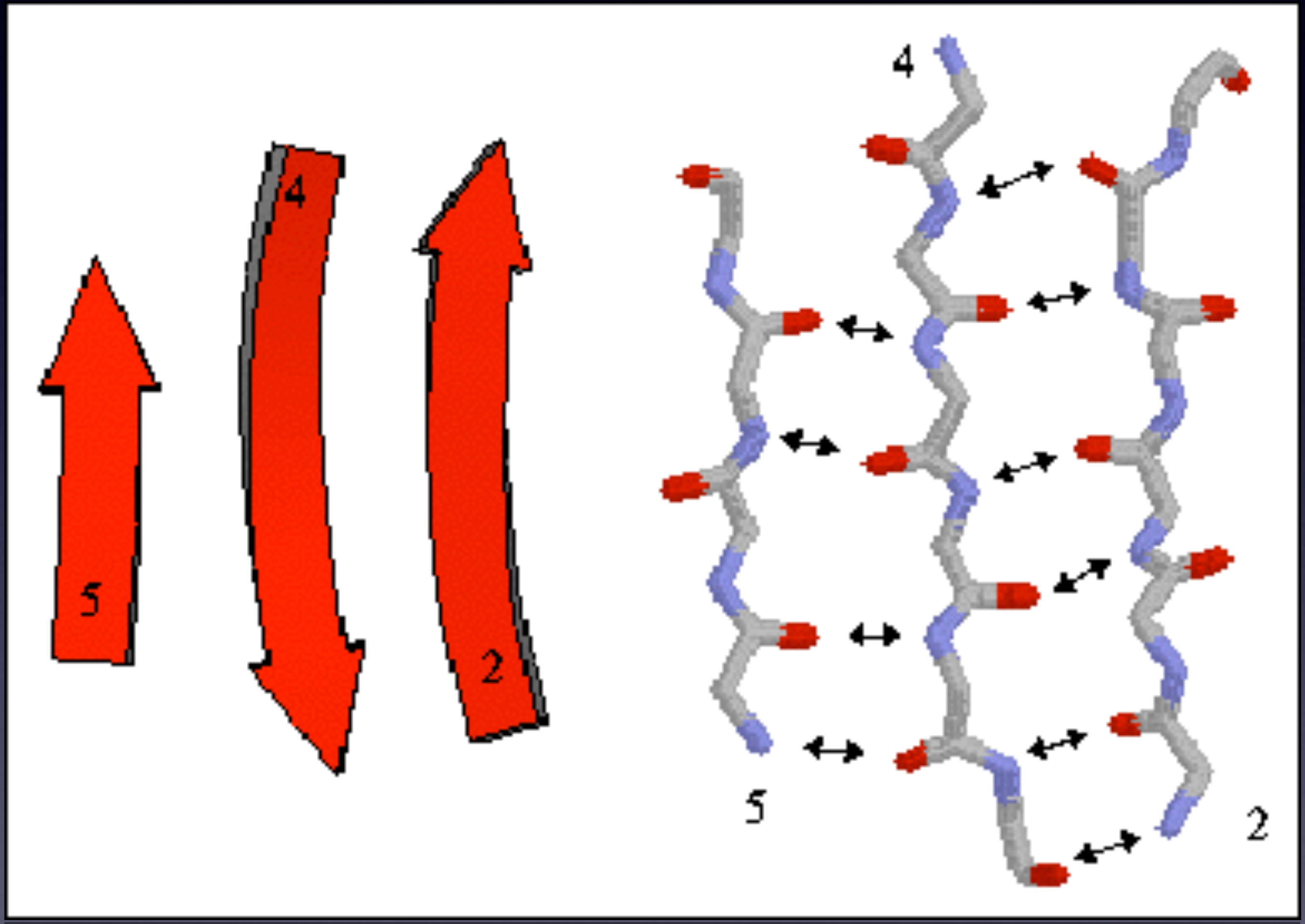


- Local structure is very ordered
  - Helices
  - Sheets
  - Turns
- Stable building blocks
  - Paired hydrogen bonds
  - Good local packing
  - No interference of side chains

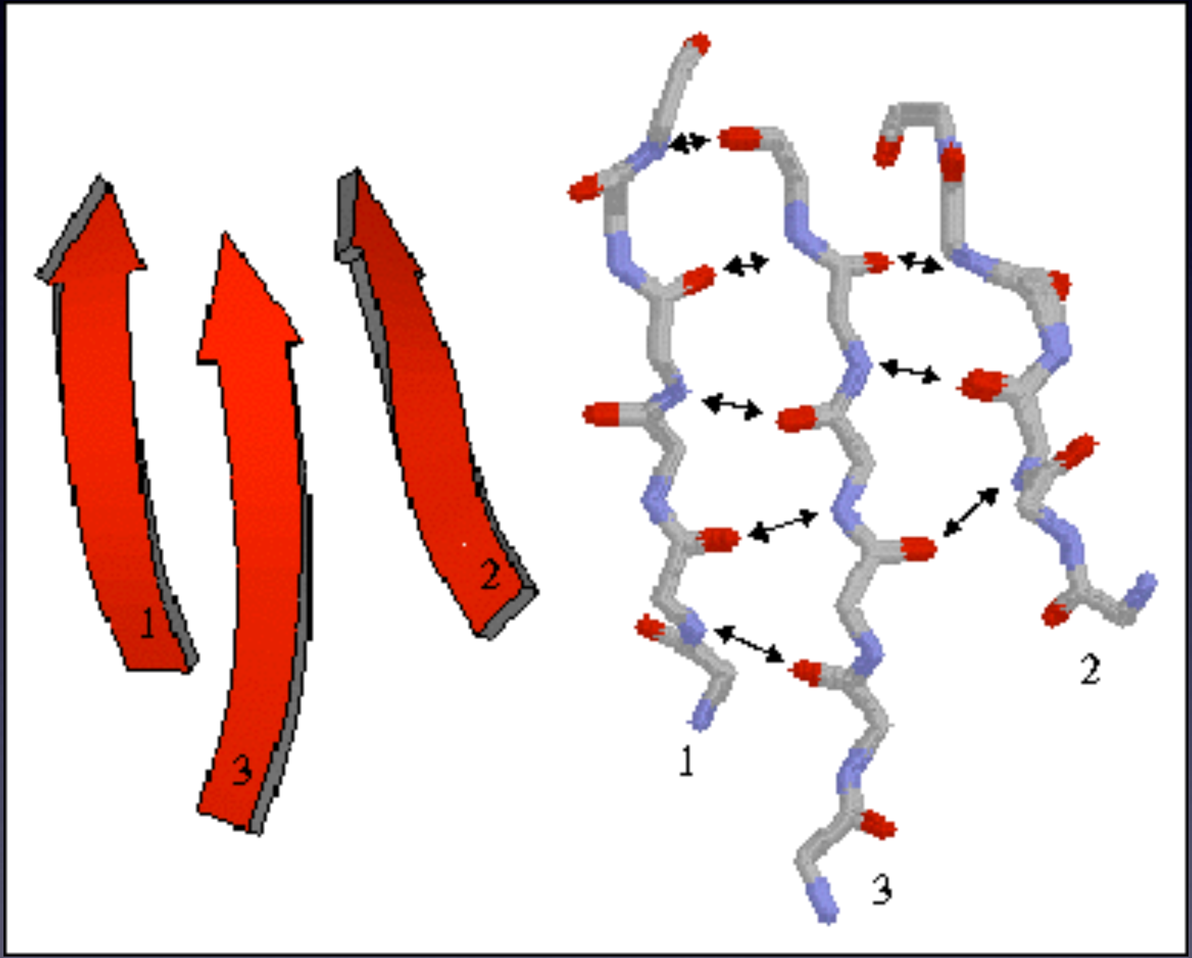


Beta sheets



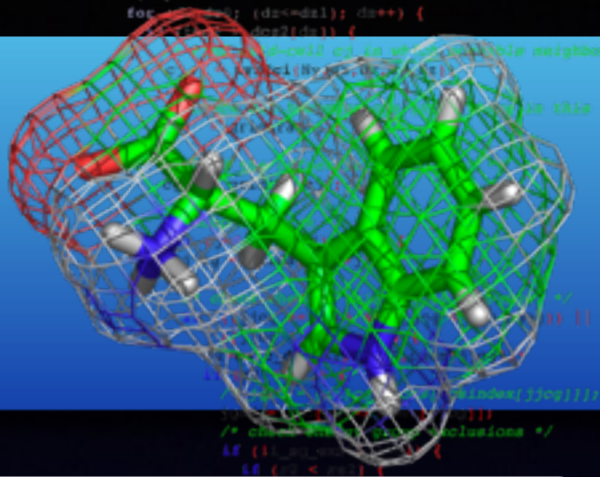


Antiparallel sheets

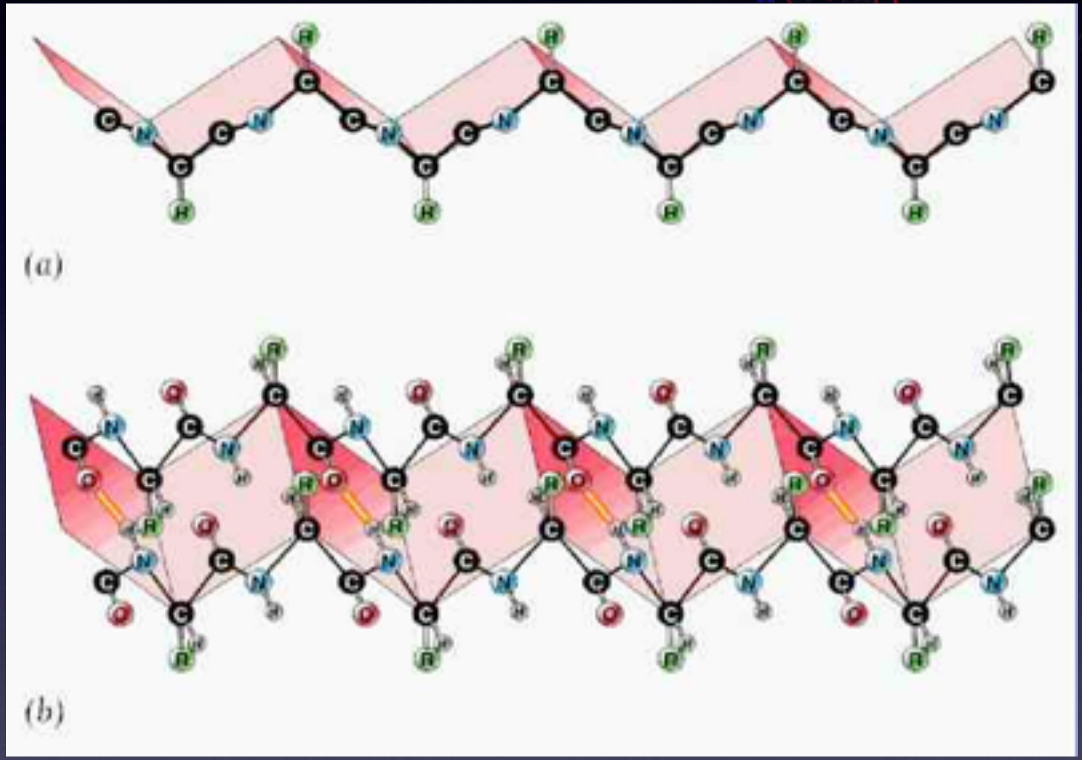


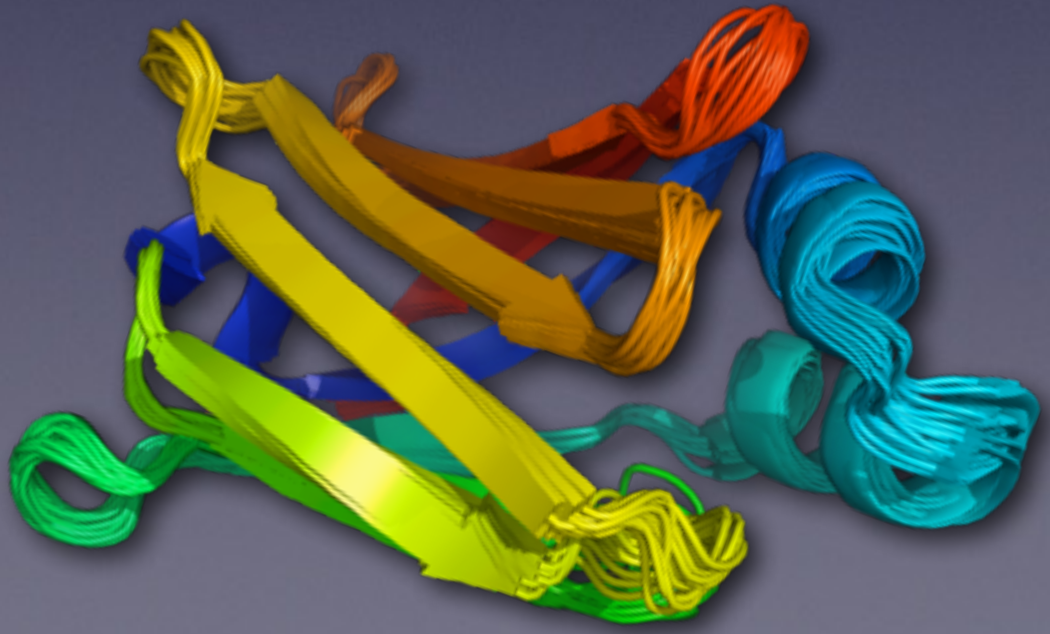
Parallel sheets

Beta sheets



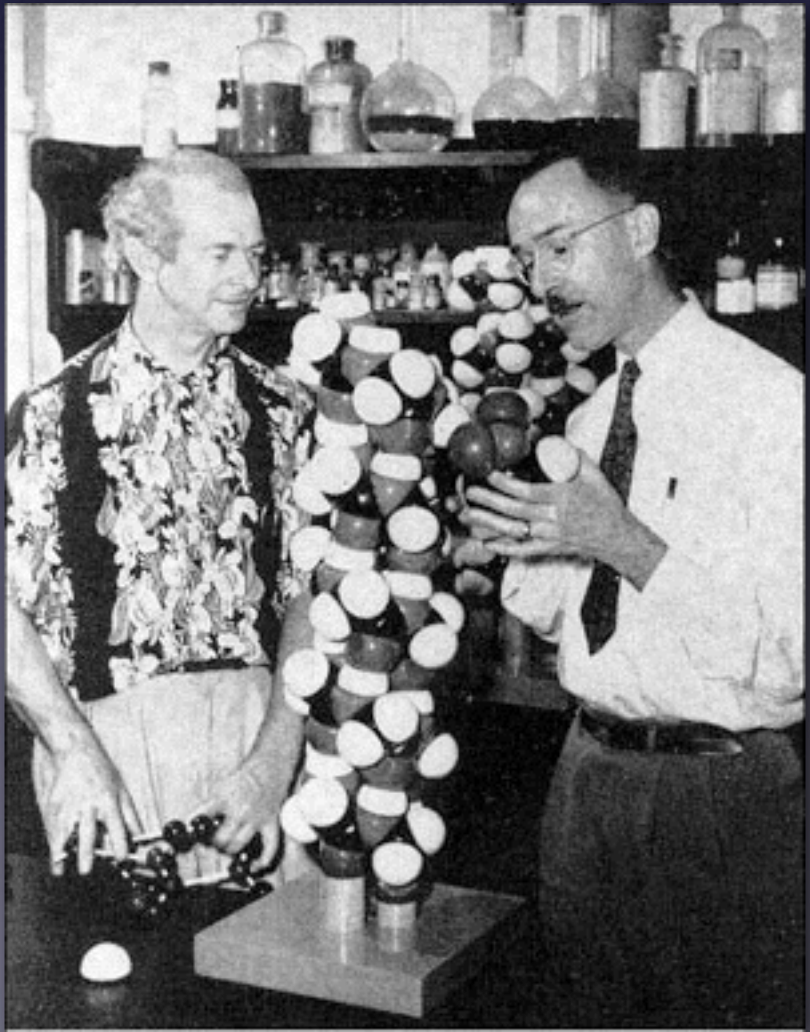
- Extended chains
- H-bonds between, not inside individual chains
- Pleated sheets
- Slightly twisted (both for strand & sheet)





Helix & sheet discovery

- Pauling, Corey (and partly Branson) - 1951
- “The protein papers” (8 papers in PNAS vol 37)
- reviewed by David Eisenberg (hand out)



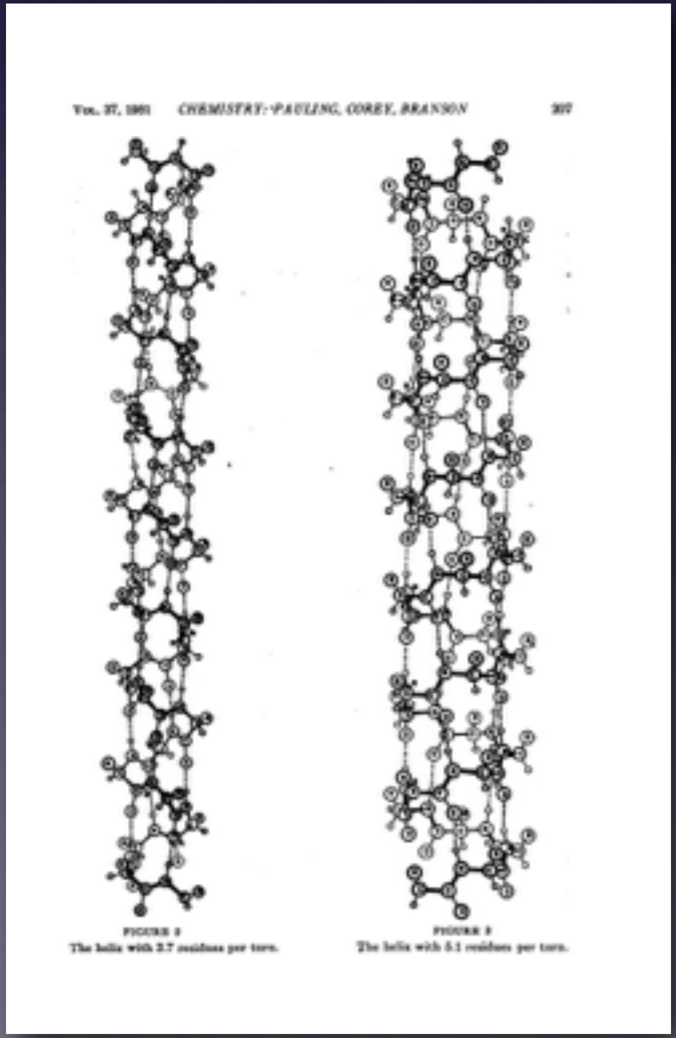


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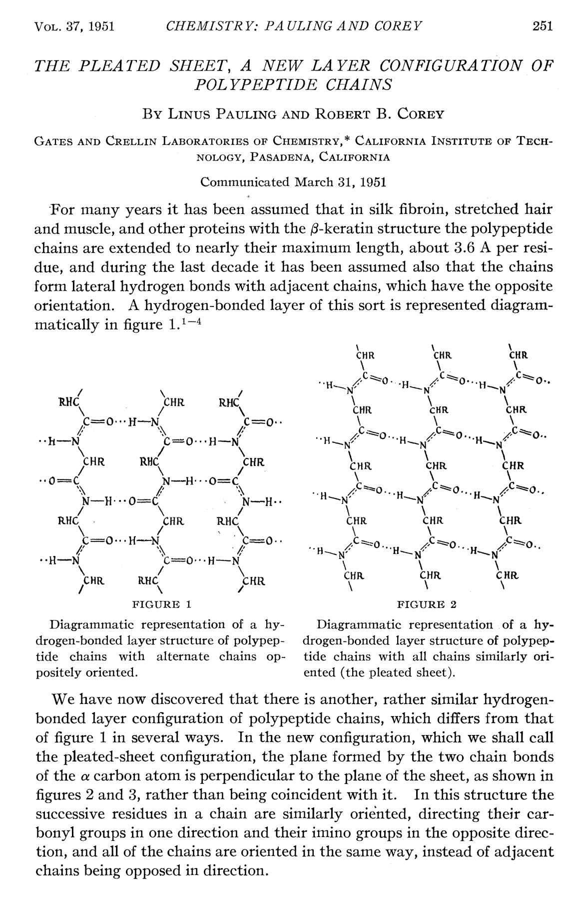
FIGURE 2

The helix with 3.7 residues per turn.

FIGURE 3

The helix with 5.1 residues per turn.



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THE PLEATED SHEET, A NEW LAYER CONFIGURATION OF POLYPEPTIDE CHAINS

By Linus Pauling and Robert B. Corey

Gates and Crellin Laboratories of Chemistry,* California Institute of Technology, Pasadena, California

Communicated March 31, 1951

For many years it has been assumed that in silk fibroin, stretched hair and muscle, and other proteins with the β-keratin structure the polypeptide chains are extended to nearly their maximum length, about 3.6 A per residue, and during the last decade it has been assumed also that the chains form lateral hydrogen bonds with adjacent chains, which have the opposite orientation. A hydrogen-bonded layer of this sort is represented diagrammatically in figure 1.[1–4]

FIGURE 1

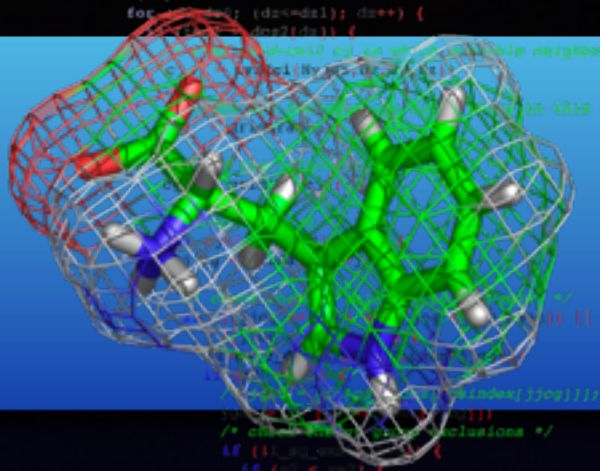
Diagrammatic representation of a hydrogen-bonded layer structure of polypeptide chains with alternate chains oppositely oriented.

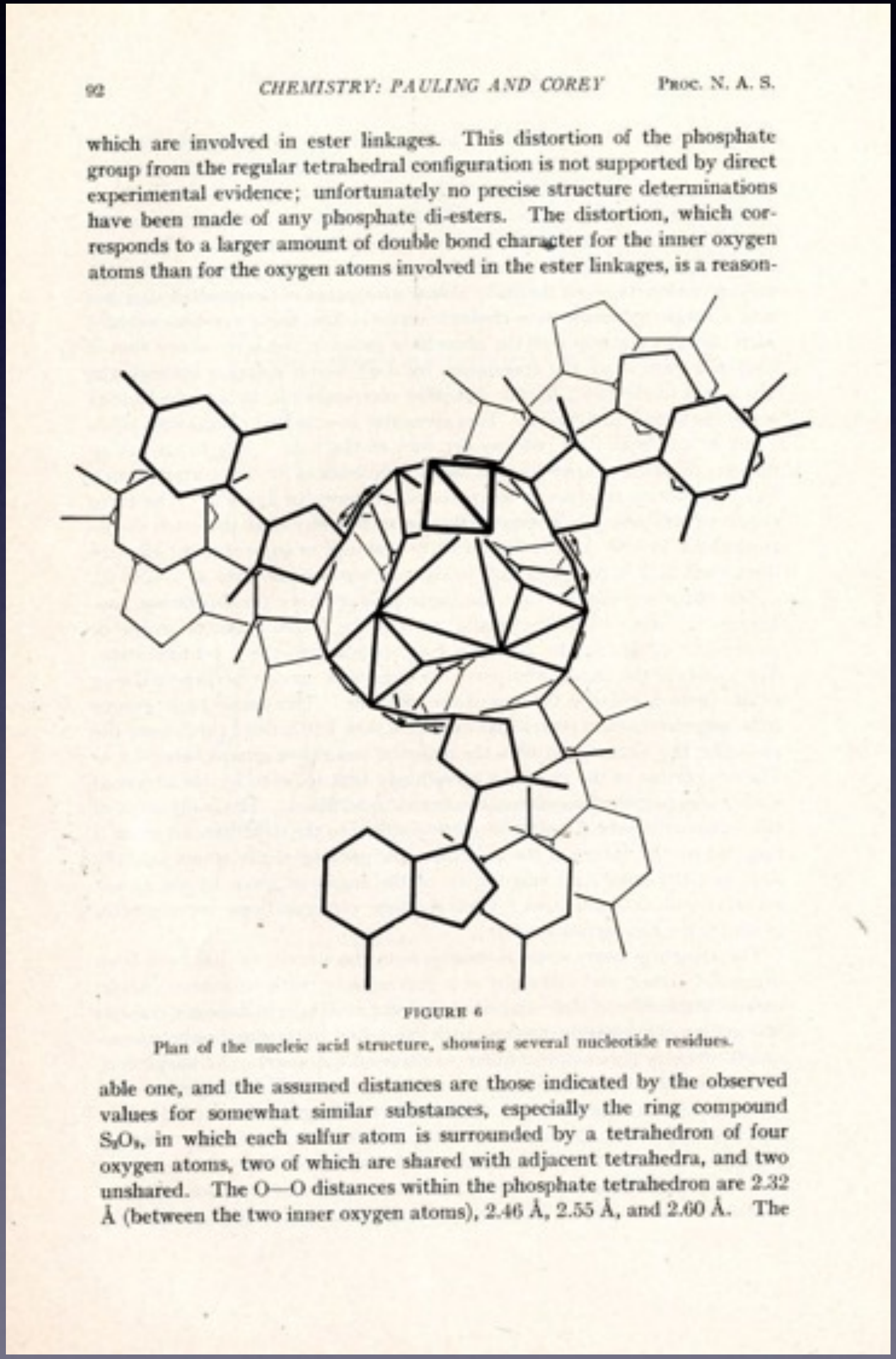
FIGURE 2

Diagrammatic representation of a hydrogen-bonded layer structure of polypeptide chains with all chains similarly oriented (the pleated sheet).

We have now discovered that there is another, rather similar hydrogen-bonded layer configuration of polypeptide chains, which differs from that of figure 1 in several ways. In the new configuration, which we shall call the pleated-sheet configuration, the plane formed by the two chain bonds of the α carbon atom is perpendicular to the plane of the sheet, as shown in figures 2 and 3, rather than being coincident with it. In this structure the successive residues in a chain are similarly oriented, directing their carbonyl groups in one direction and their imino groups in the opposite direction, and all of the chains are oriented in the same way, instead of adjacent chains being opposed in direction.

Pauling DNA





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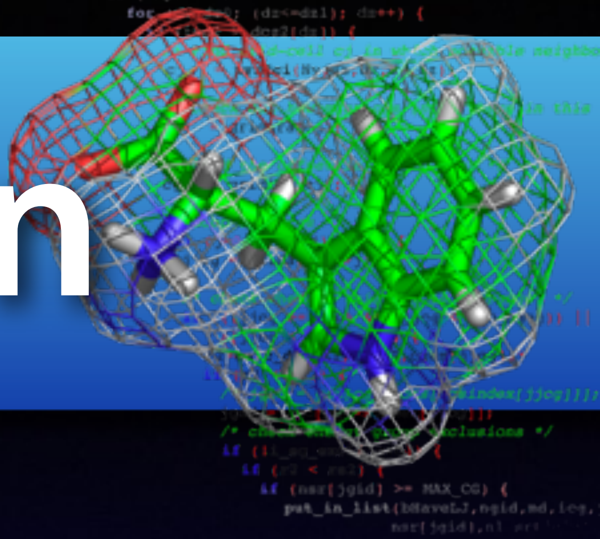
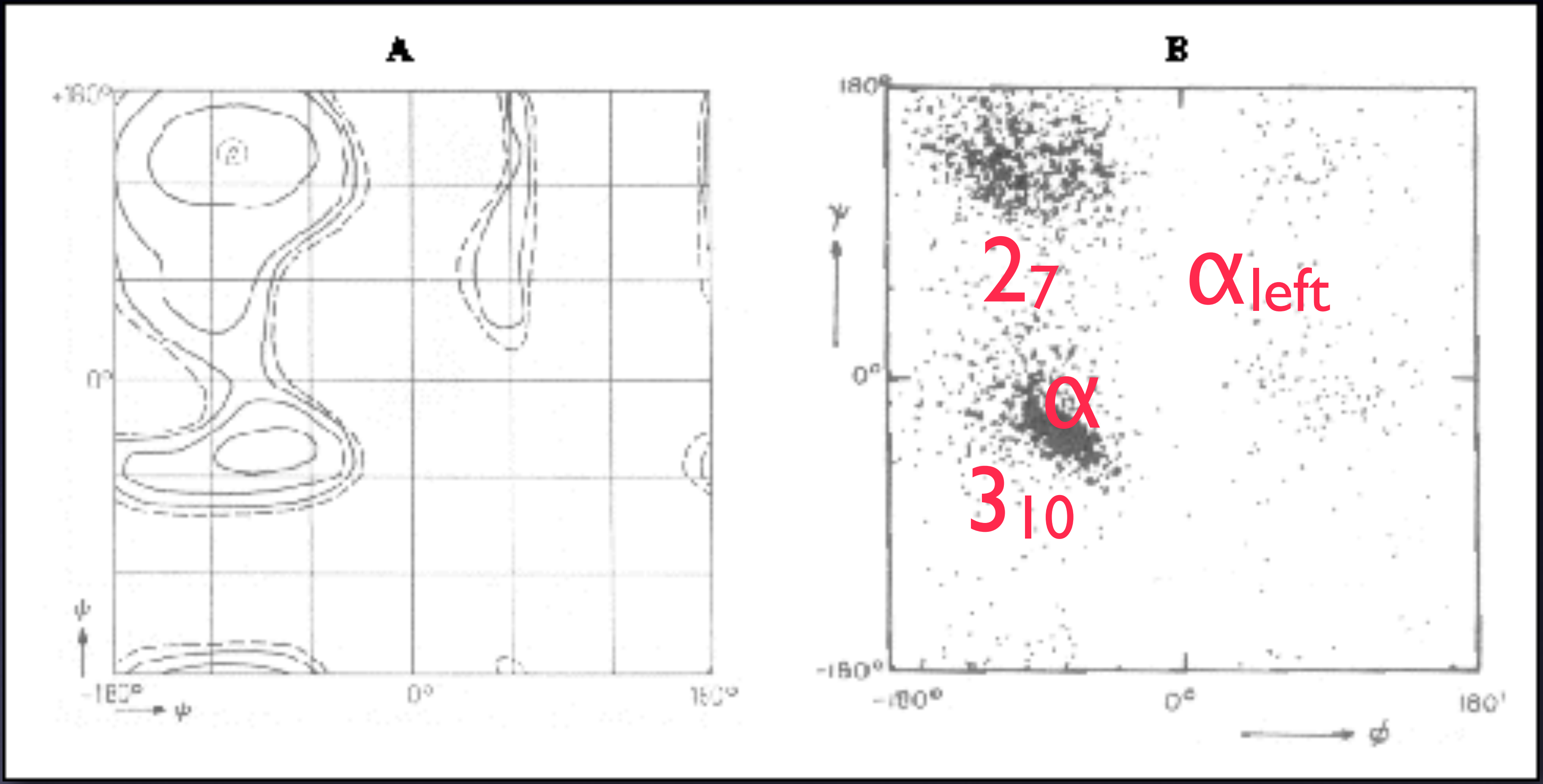
which are involved in ester linkages. This distortion of the phosphate group from the regular tetrahedral configuration is not supported by direct experimental evidence; unfortunately no precise structure determinations have been made of any phosphate di-esters. The distortion, which corresponds to a larger amount of double bond character for the inner oxygen atoms than for the oxygen atoms involved in the ester linkages, is a reasonable one, and the assumed distances are those indicated by the observed values for somewhat similar substances, especially the ring compound S_3O_9, in which each sulfur atom is surrounded by a tetrahedron of four oxygen atoms, two of which are shared with adjacent tetrahedra, and two unshared. The O—O distances within the phosphate tetrahedron are 2.32 Å (between the two inner oxygen atoms), 2.46 Å, 2.55 Å, and 2.60 Å. The

FIGURE 6

Plan of the nucleic acid structure, showing several nucleotide residues.

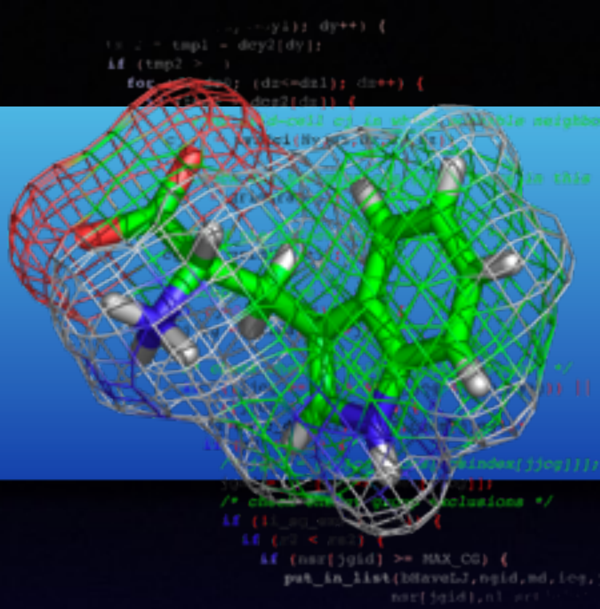
Ramachandran, again

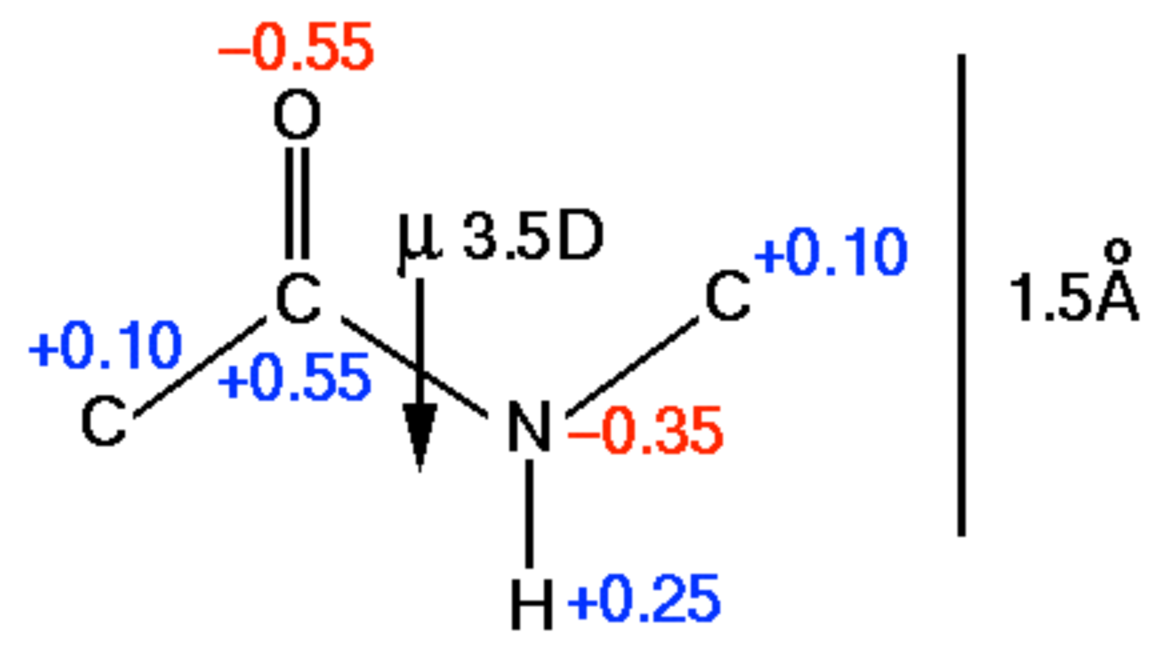


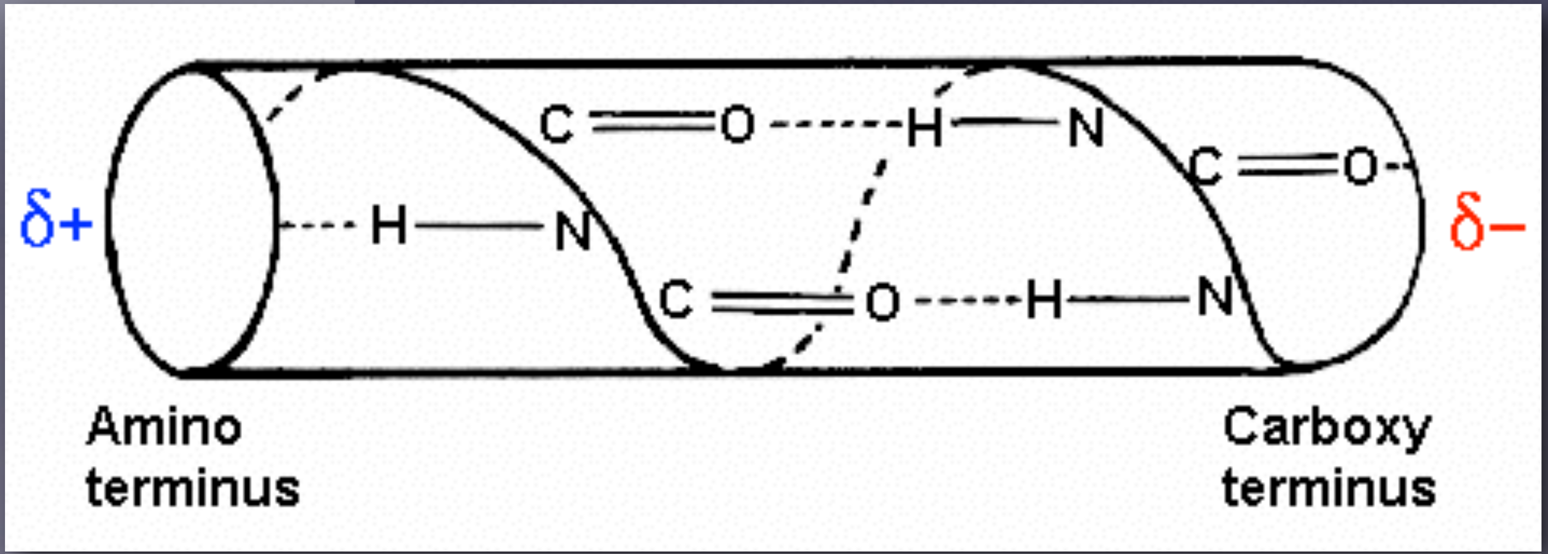


- α-helices occupy favorable part of diagram
- 3.6 residues per turn (100 degrees per residue)

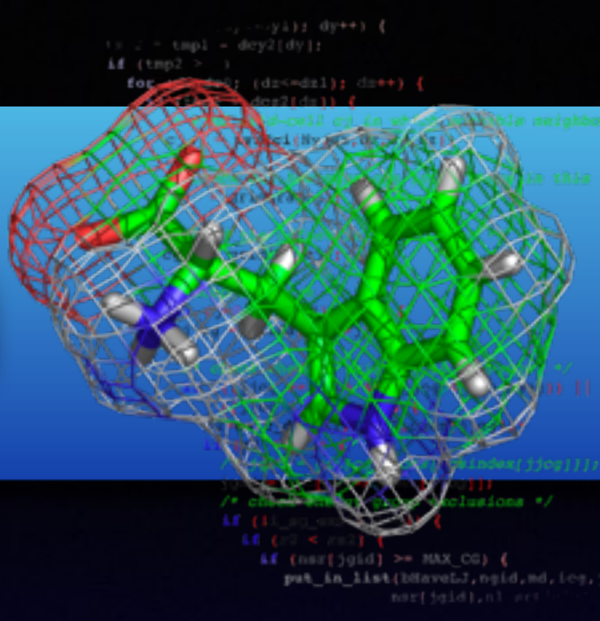
Helix dipoles

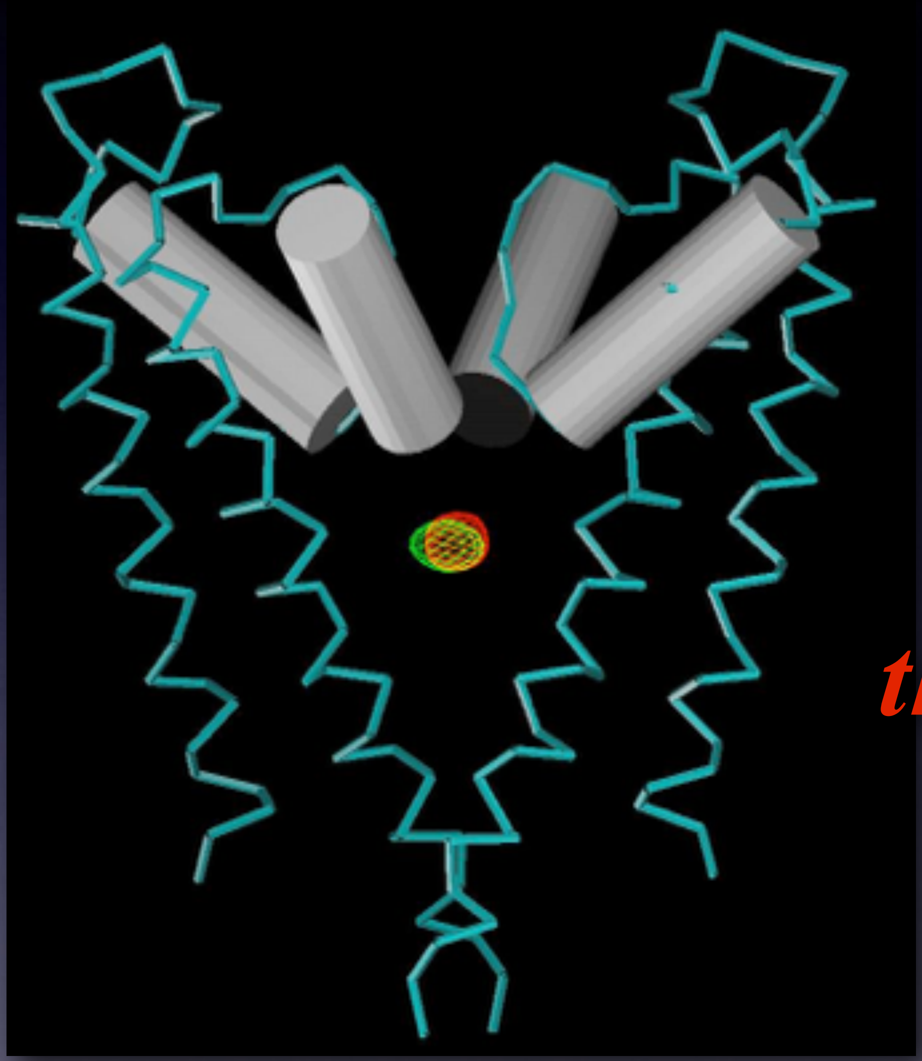






KcsA ion stabilization





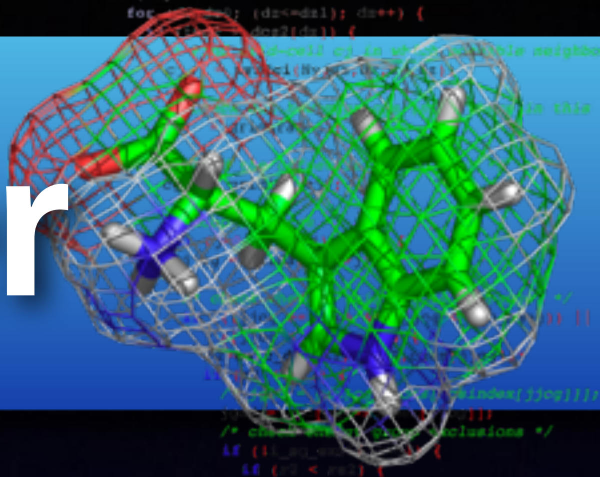
KcsA

How can a K^+ ion pass through the membrane almost without barriers?

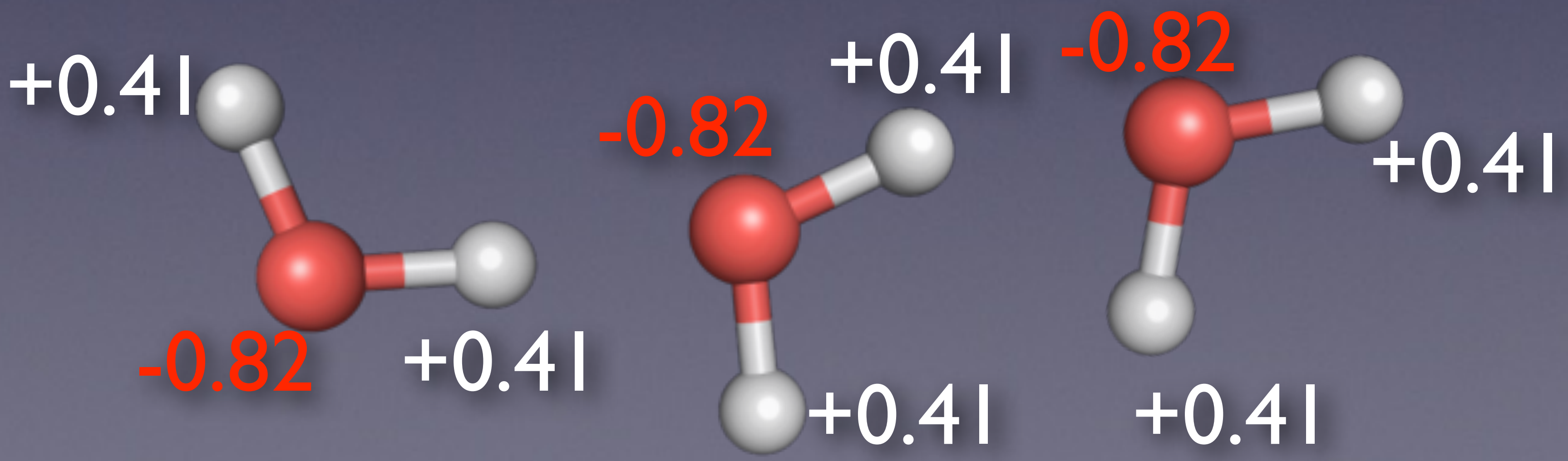
AND: How can potassium pass, but not sodium which has a smaller radius!?

Roux & McKinnon, 1999

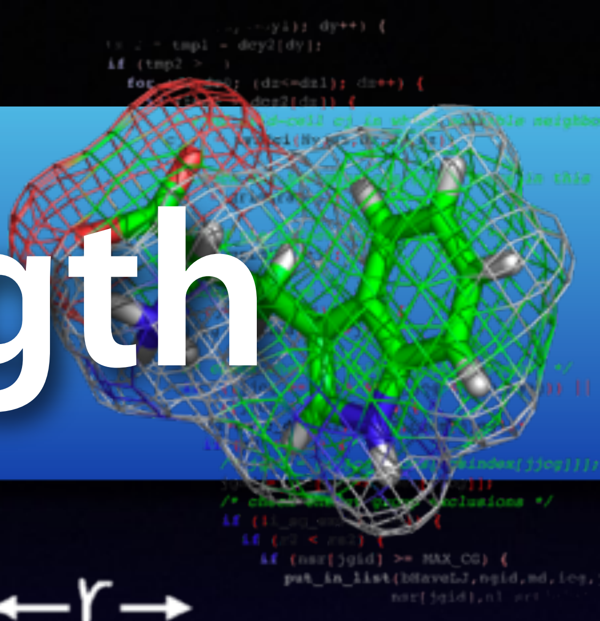
H-bonds in Water



- Extremely high freezing & boiling points compared to similar molecules (O_2,CH_4)
- All due to the hydrogen bonds

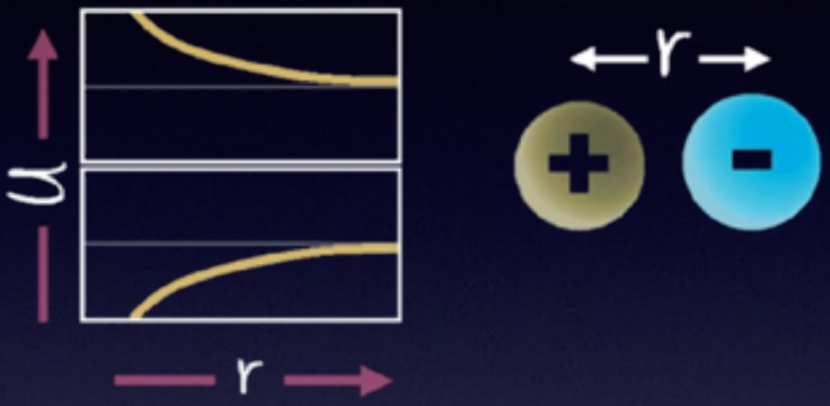


Electrostatic strength



$$+\sum 332 q_i q_j / r$$

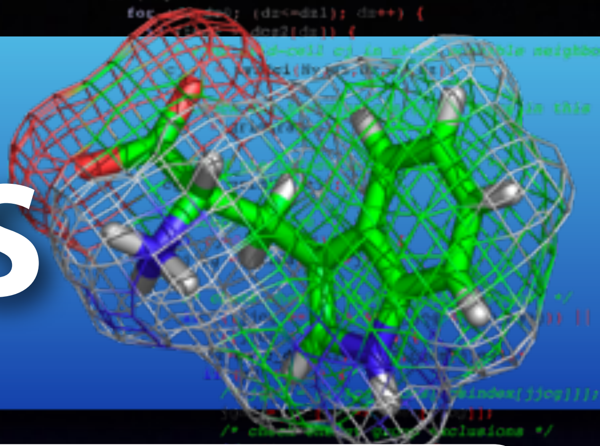
All partial charges

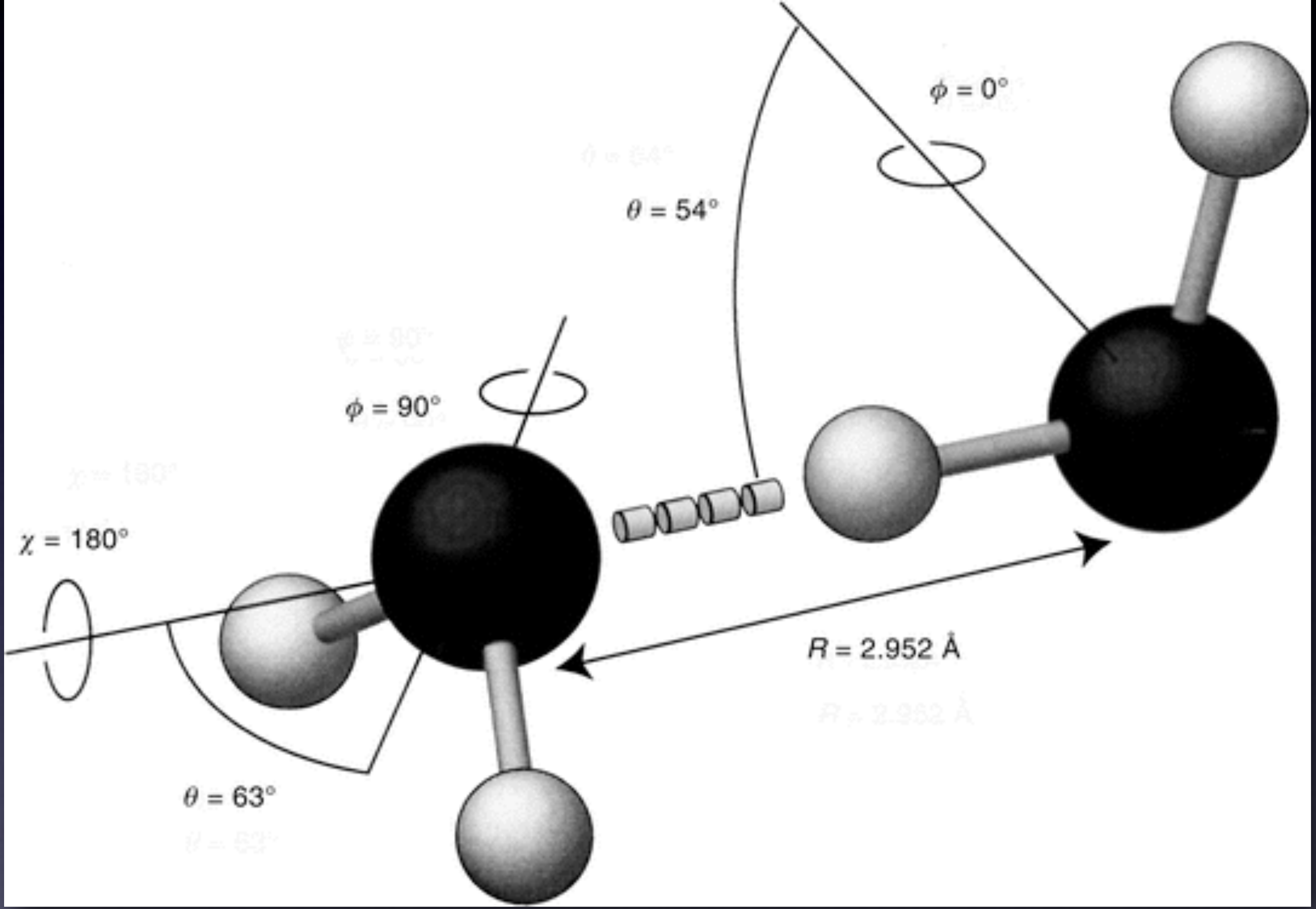


Example interaction energy:
Two charges separated by ~1Å: 330 kcal/mol!
(Compare to bond rotation, 2-4 kcal)

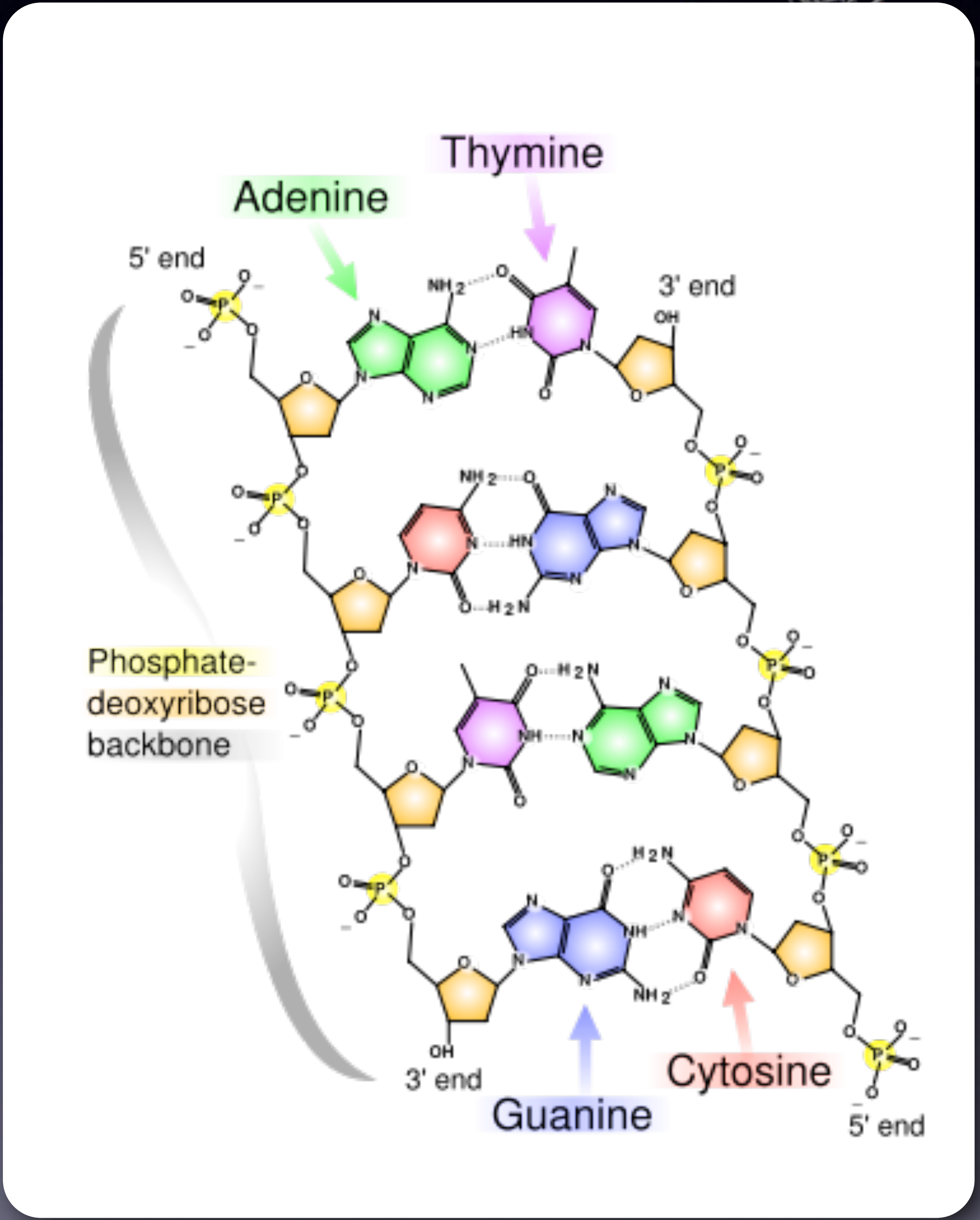
Electrostatic interactions decay as 1/r (slow!)

Hydrogen bonds





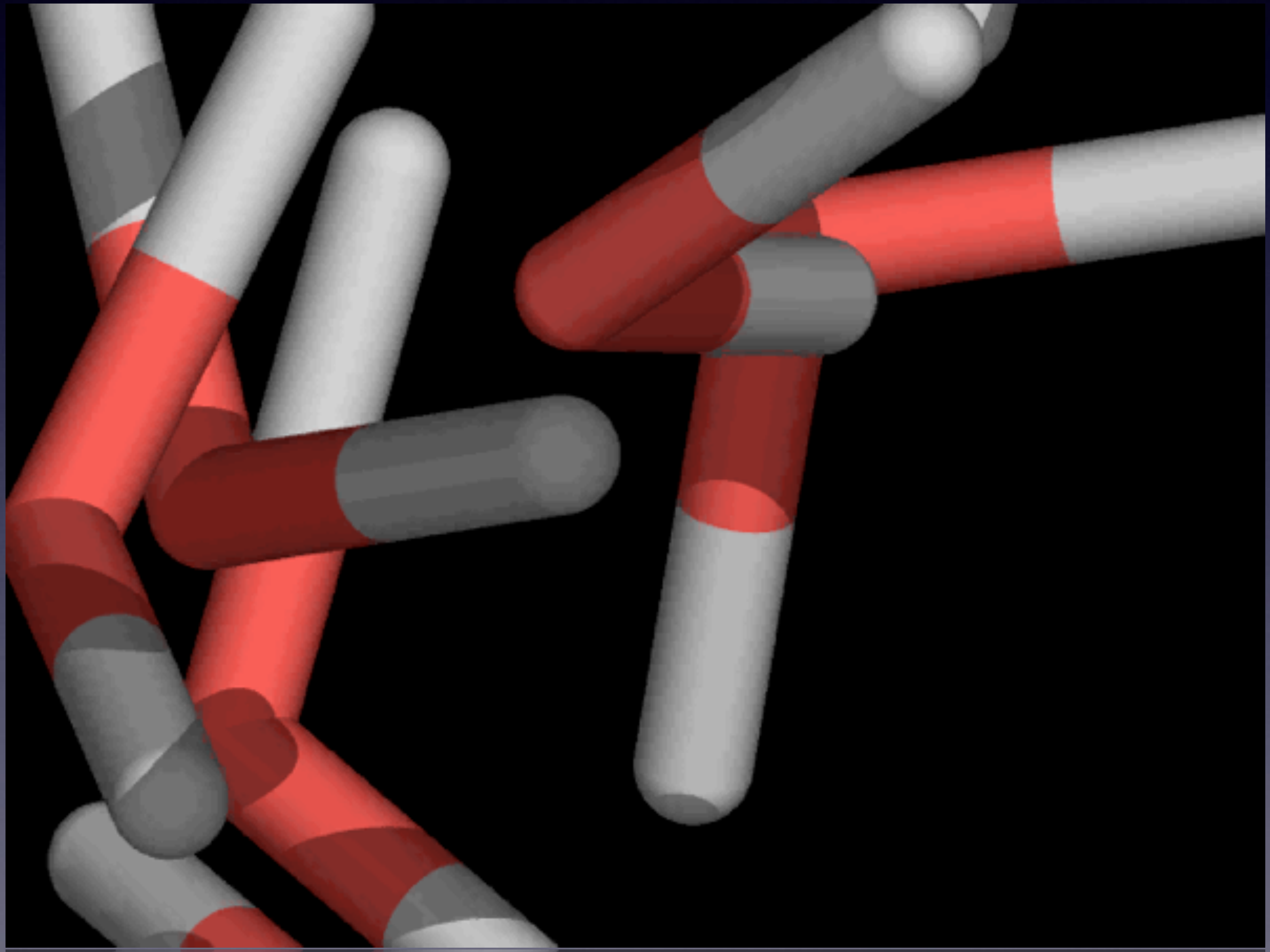
O-H or N-H group is donor
Other O group is acceptor
Donor group is very directional:
max 30 degrees offset!



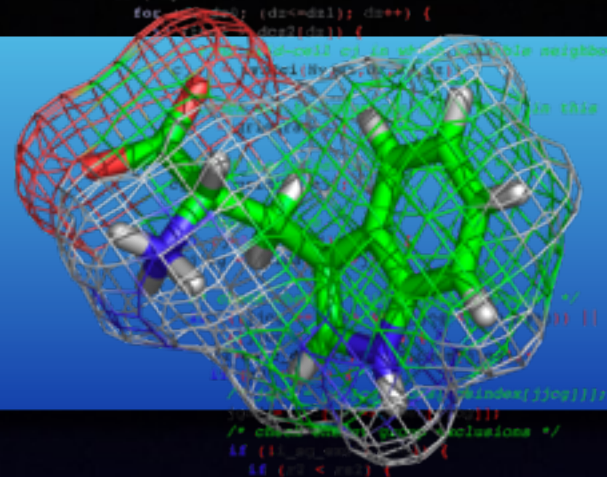
5 kcal/mol energy!

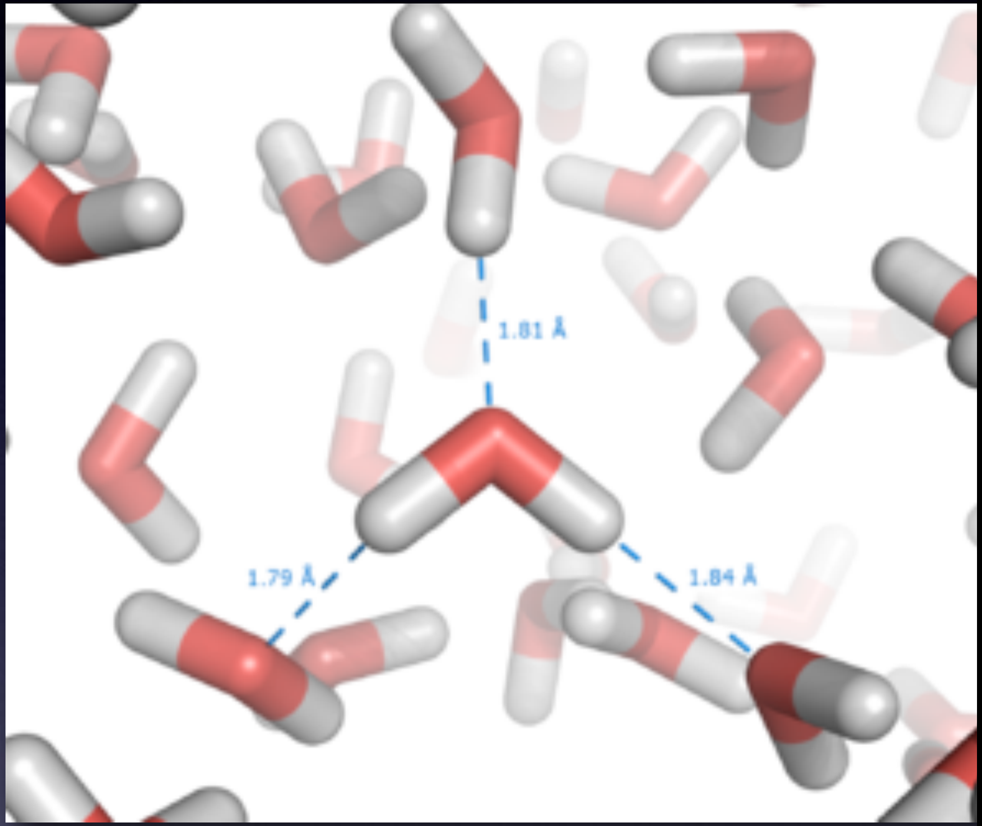
Water

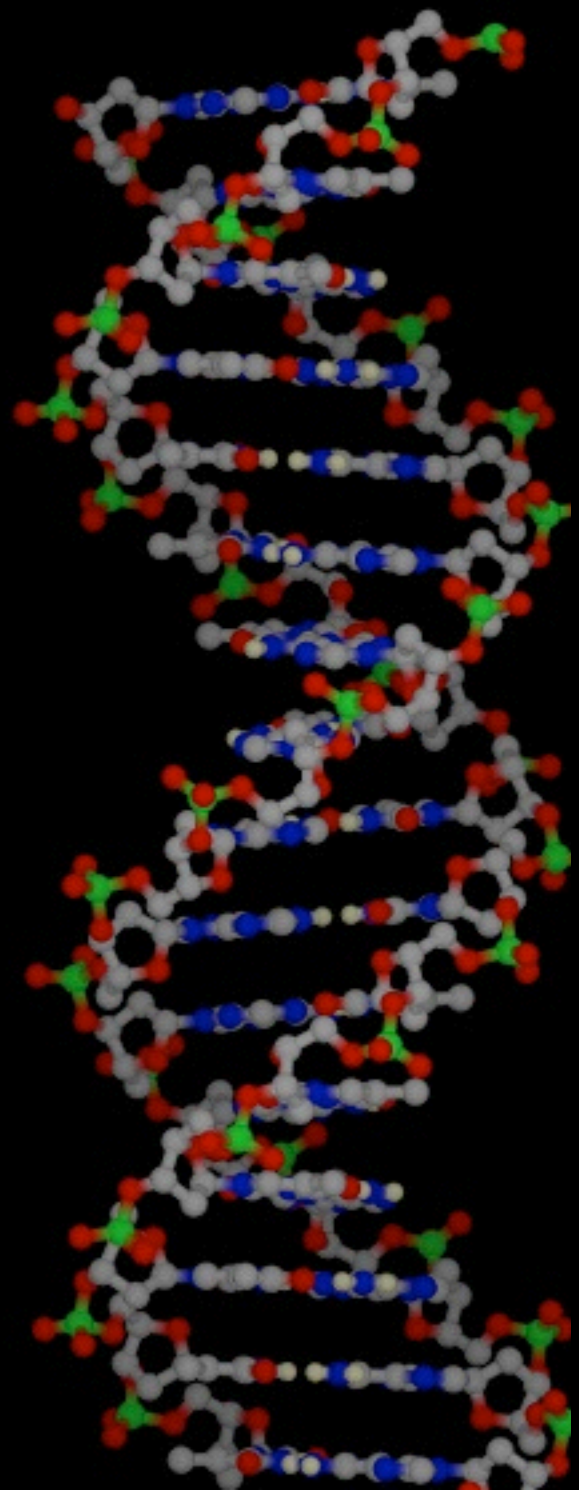
Virtually all h-bonds are intact!
(1.7 per water)

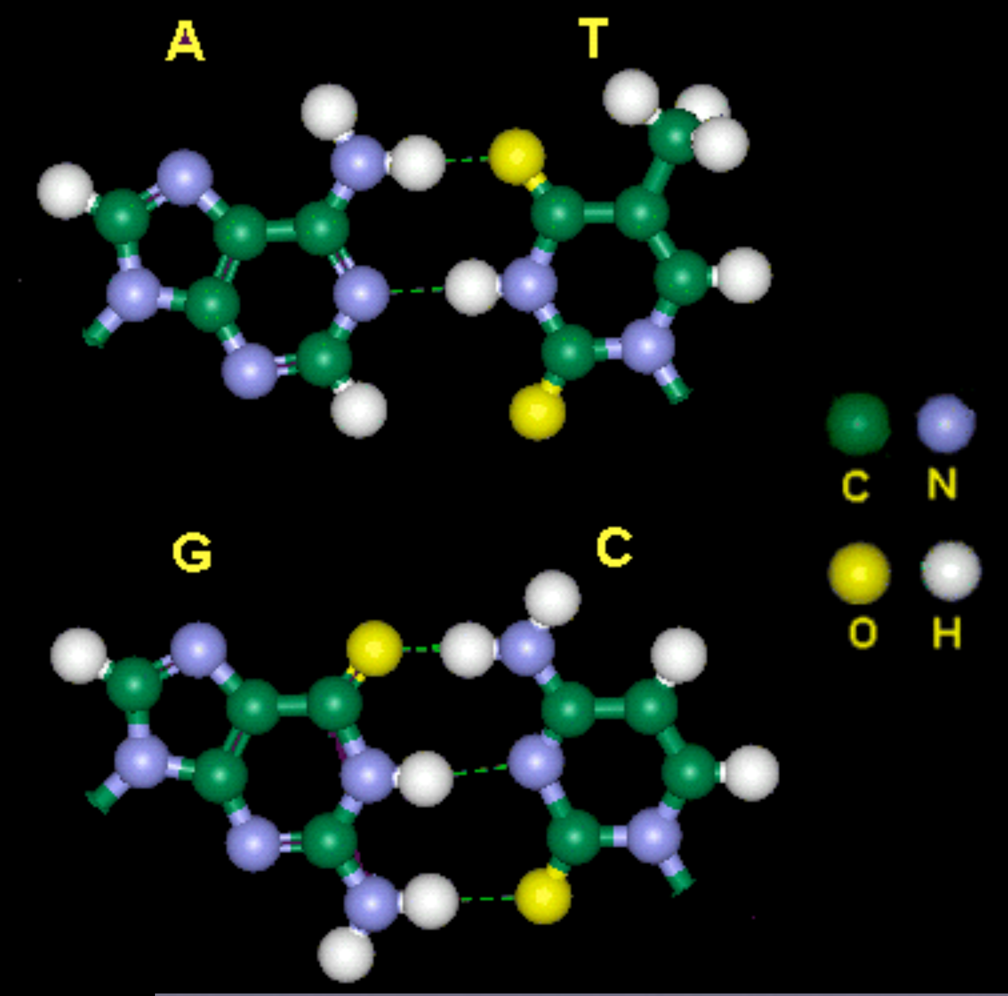


Hydrogen bonds

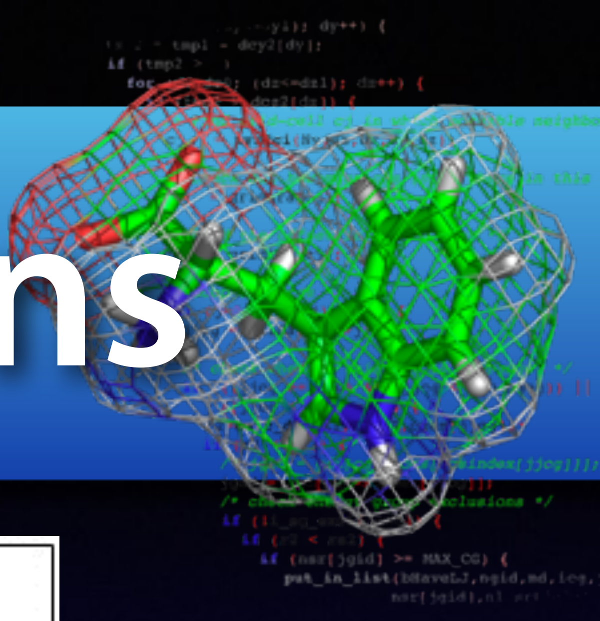


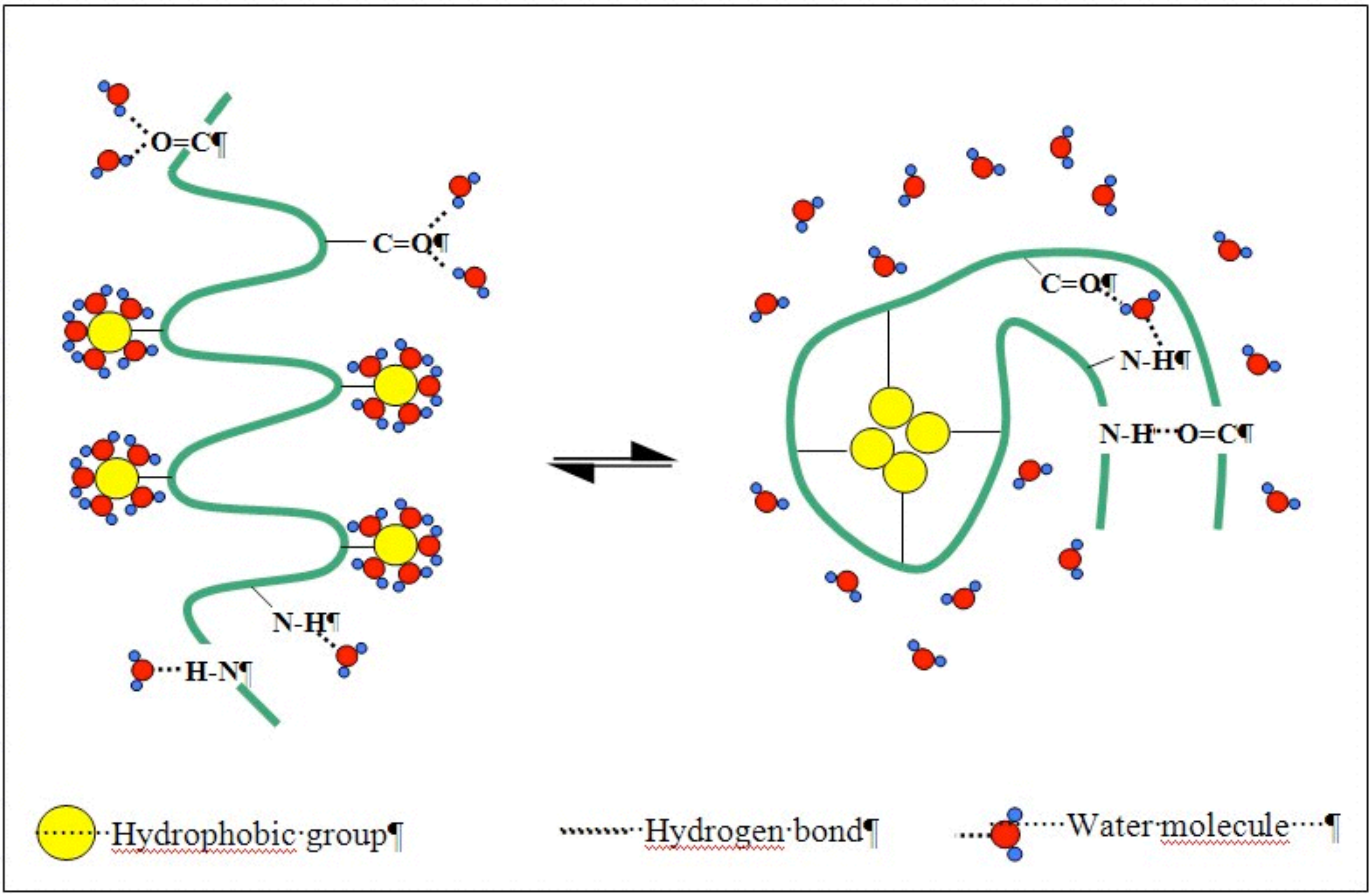




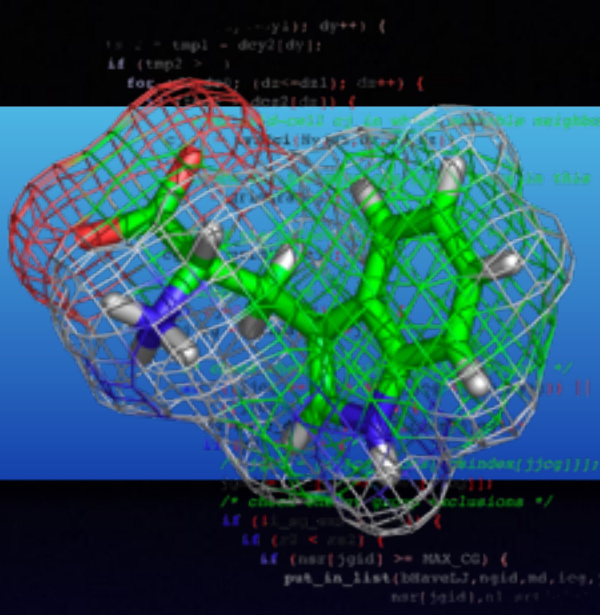


H-bonds in proteins



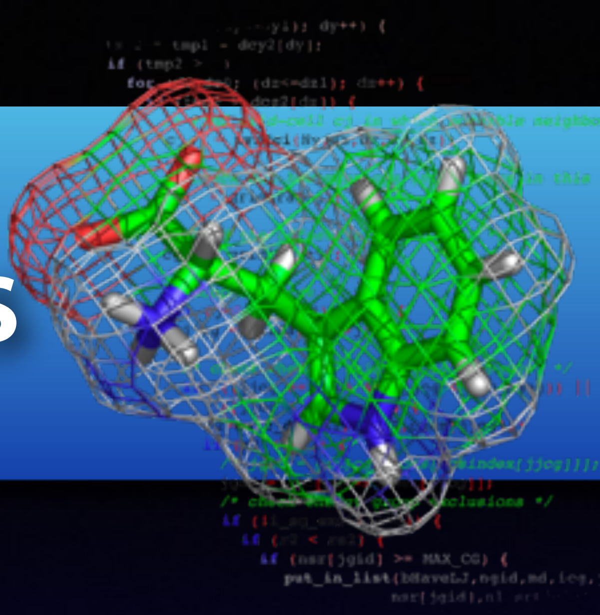


Summary



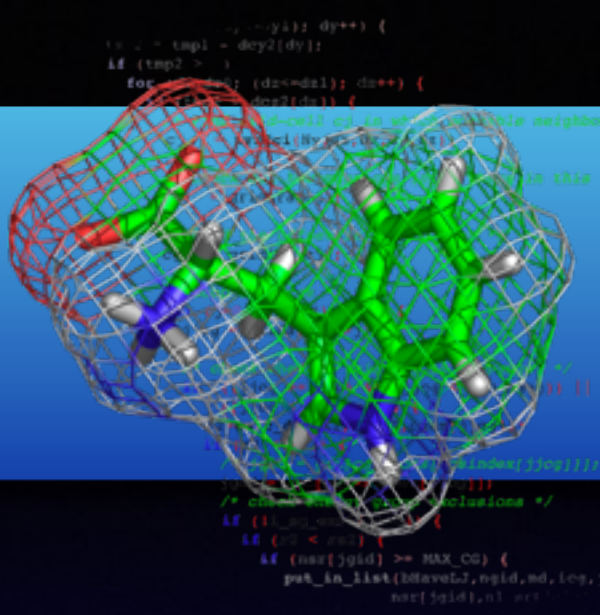
- Read chapters 1-2 of "Protein Physics"
  - Understand amino acids, conformations
  - Understand hydrogen bonds
- Anfinsen & Levinthal - what did they say?
- Questions?

Advice from fellow students



- “Attending the class helps a lot in understanding the book contents”
- “Start reading in the beginning! Try to read the covered chapters the same day or week”
- “Go to the lectures I guess. I didn’t and it was really hard to read the course yourself”

For Lecture 2



- More on interactions, charges & electrostatics
- Hydrogen bonds
- The peptide bond properties
- Boltzmann distribution
- Free Energy
- Definitions of entropy, temperature, etc.