

INTRODUCTION TO PROTEIN STRUCTURES

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COMPUTATIONAL BIOPHYSICS CB_23_24_L11
thu Oct 19 2023

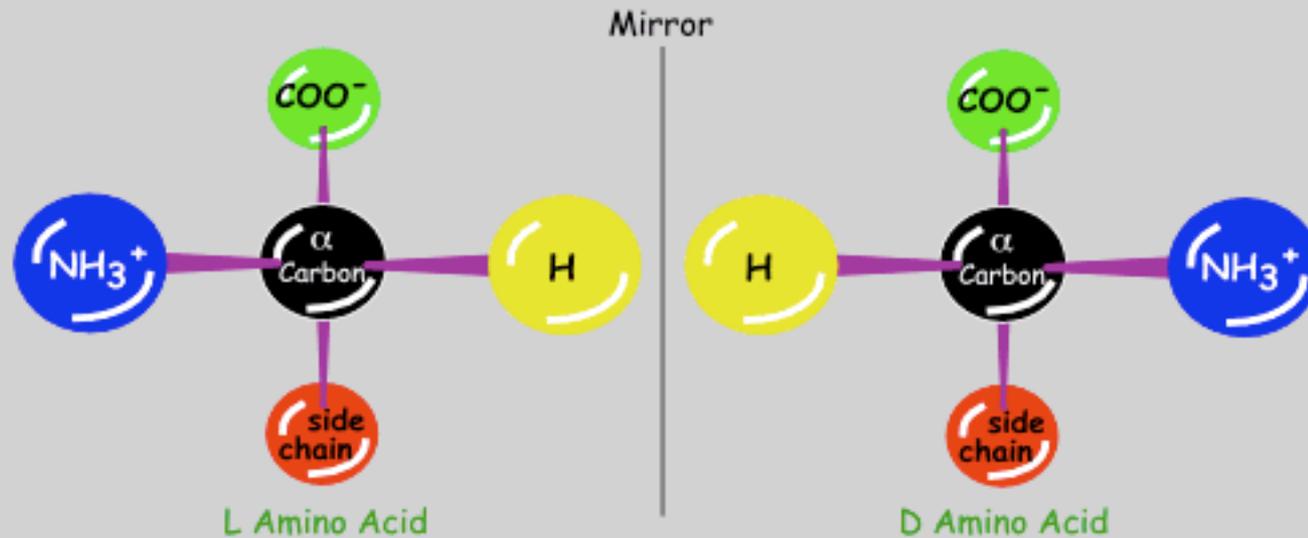
DIPARTIMENTO DI FISICA



SAPIENZA
UNIVERSITÀ DI ROMA

- SEQUENCE->STRUCTURE/UNSTRUCTURE->DYNAMICS-FUNCTIONS

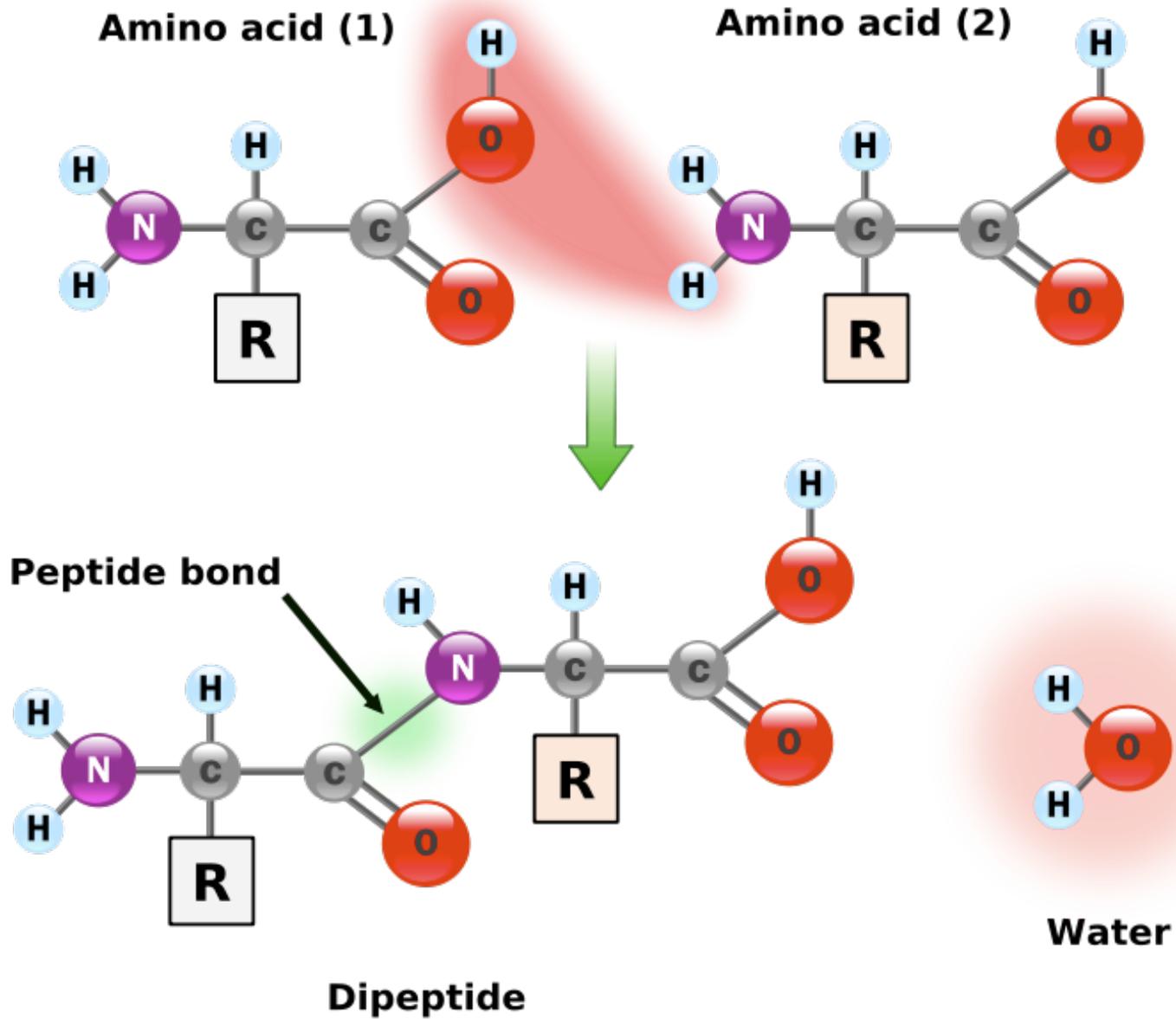
**Common Amino Acids are Stereoisomers,
Meaning they have a Chiral α Carbon center.**



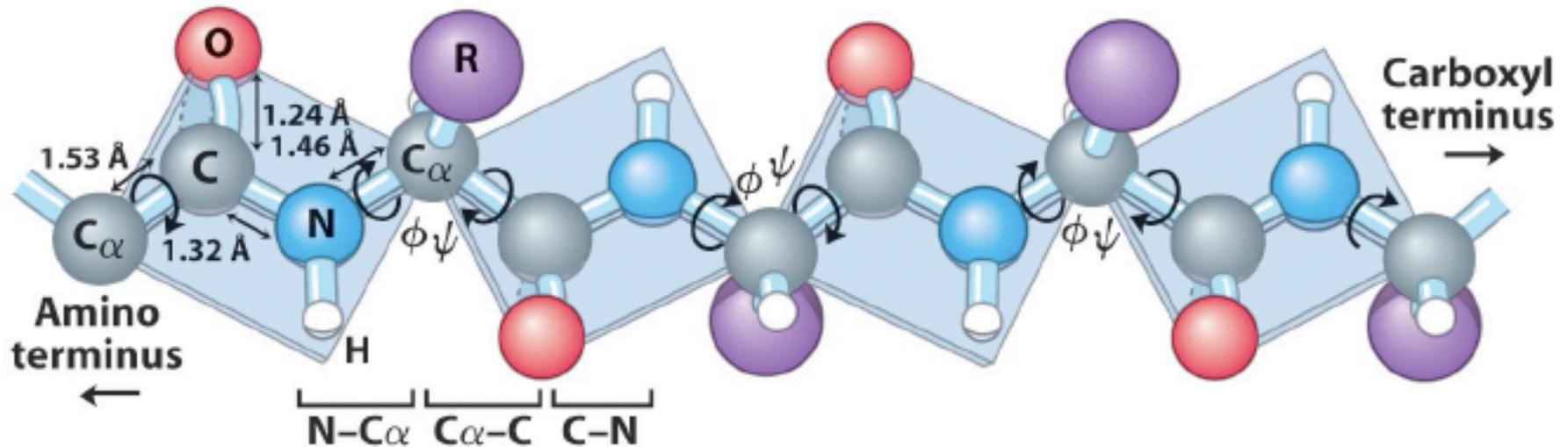
Amino Acids can exist in either the D or L configuration.
However, All Chiral Amino Acids in Proteins have the L configuration

19 out of 20 are chiral: natural state is L! Still an unsolved puzzle.
Nevertheless D-chiral enzymes are active on D-chiral substrates

PEPTIDE BOND

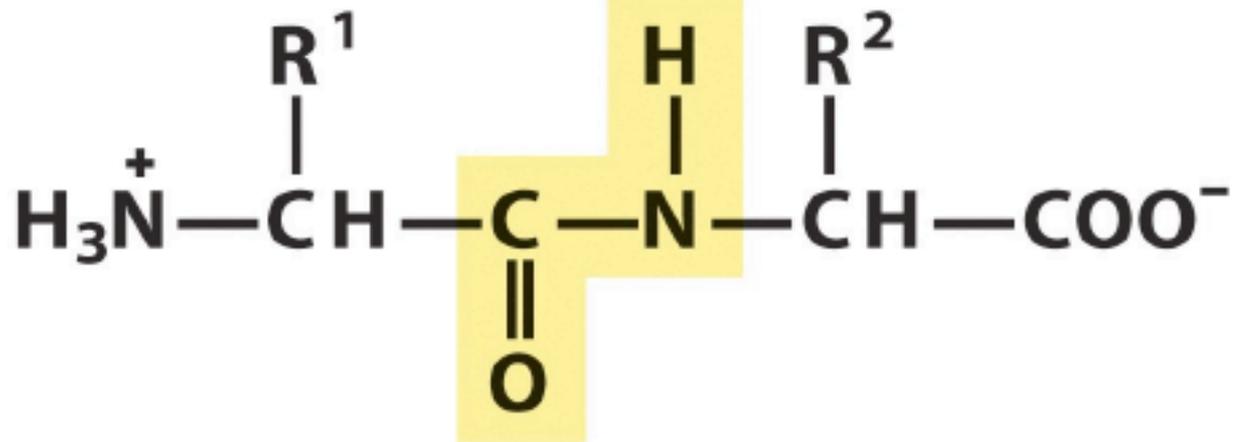
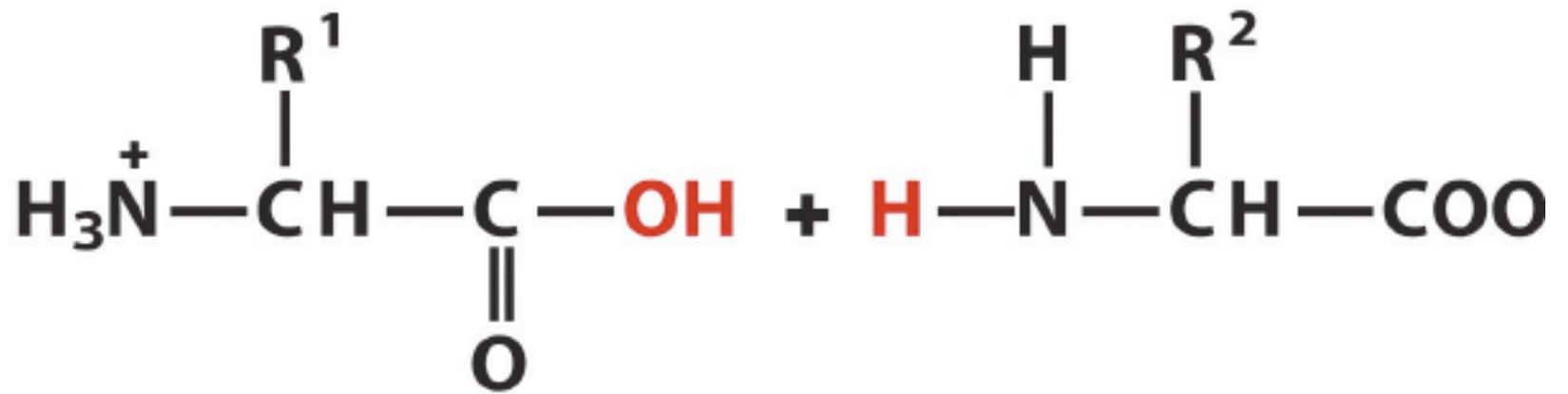


Peptide bonds are planar

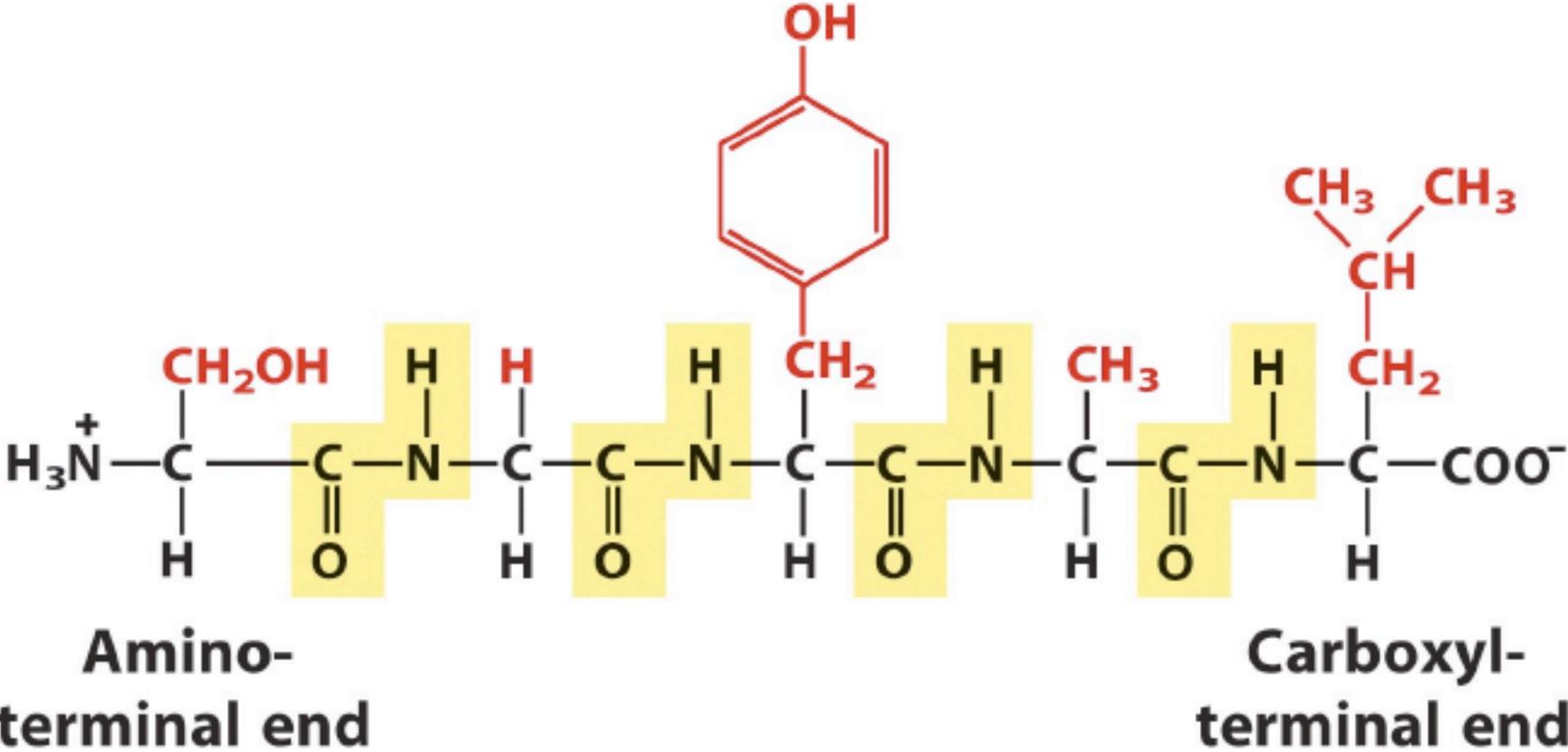


The polypeptide backbone (main chain) refers to atoms that participate in peptide bonds, and can be drawn as a linked set of rigid planar groups.

Two torsion angles, phi and psi, describe backbone conformation.

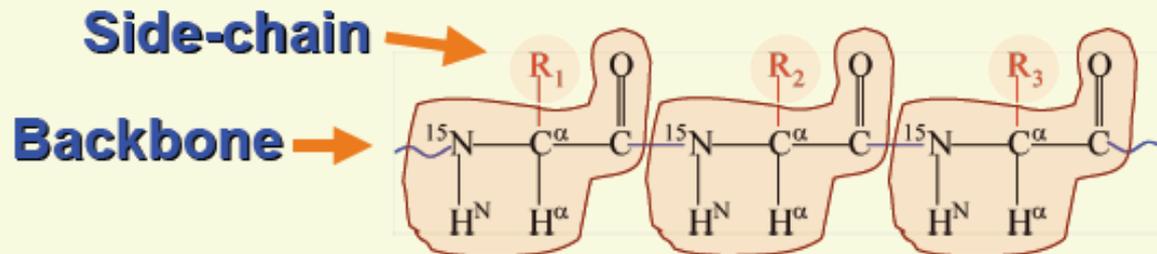


Generally a protein initiates with a Methionine



Protein Structure

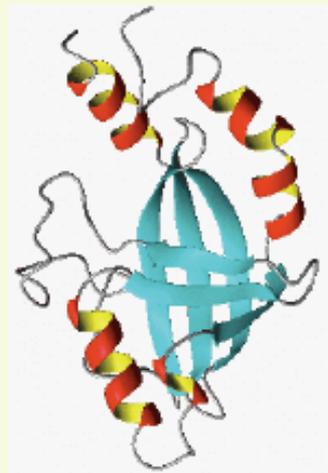
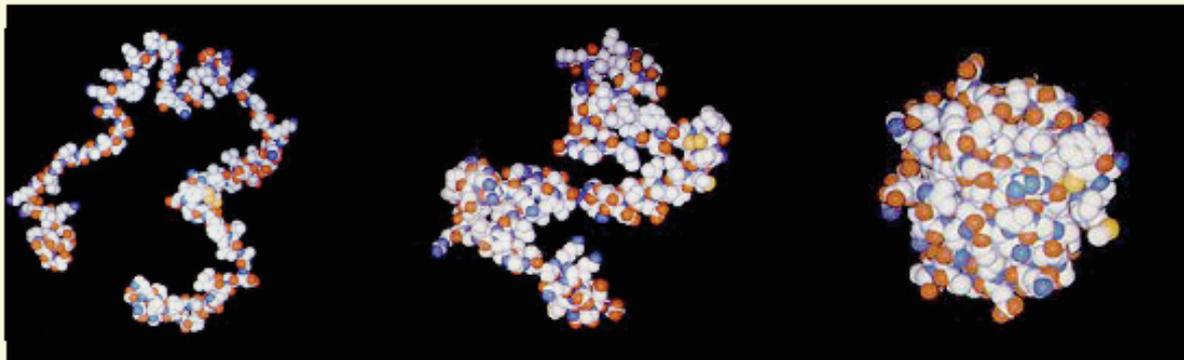
Primary Sequence: Linear String of Amino Acids

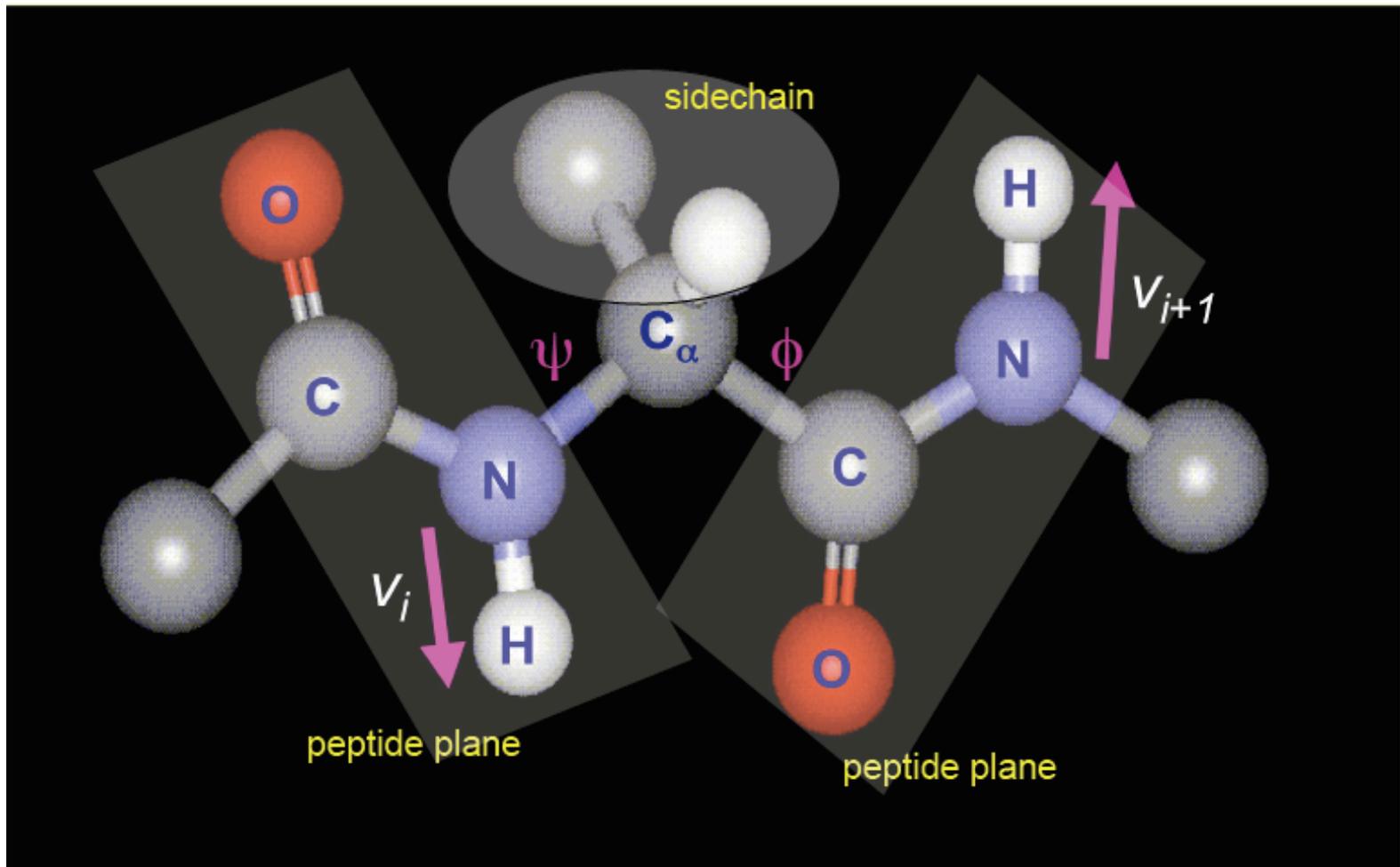


Secondary structure: regular α -helices and β -strands

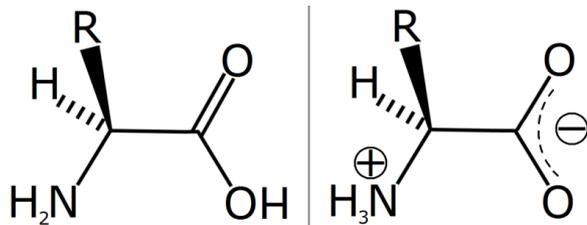
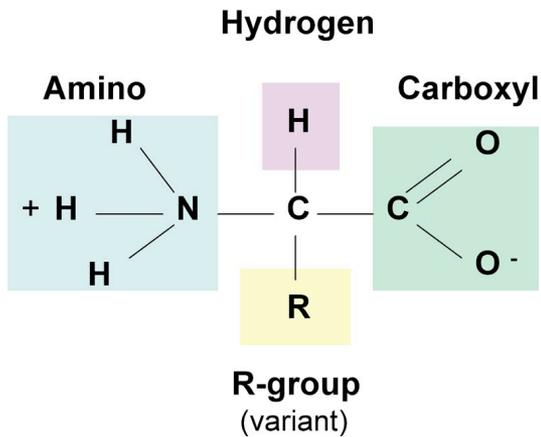


Global Fold





Amino Acid Structure



NONPOLAR, HYDROPHOBIC

POLAR, UNCHARGED

R GROUPS

Alanine Ala A MW = 89	$\begin{matrix} ^- \text{OOC} \\ \\ \text{H}_3\text{N}^+ \end{matrix} \text{CH} - \text{CH}_3$	$\text{H} - \text{CH} - \begin{matrix} \text{COO}^- \\ \\ \text{N}^+ \text{H}_3 \end{matrix}$	Glycine Gly G MW = 75
Valine Val V MW = 117	$\begin{matrix} ^- \text{OOC} \\ \\ \text{H}_3\text{N}^+ \end{matrix} \text{CH} - \text{CH} \begin{matrix} \text{CH}_3 \\ \\ \text{CH}_3 \end{matrix}$	$\text{HO} - \text{CH}_2 - \text{CH} \begin{matrix} \text{COO}^- \\ \\ \text{N}^+ \text{H}_3 \end{matrix}$	Serine Ser S MW = 105
Leucine Leu L MW = 131	$\begin{matrix} ^- \text{OOC} \\ \\ \text{H}_3\text{N}^+ \end{matrix} \text{CH} - \text{CH}_2 - \text{CH} \begin{matrix} \text{CH}_3 \\ \\ \text{CH}_3 \end{matrix}$	$\text{OH} \begin{matrix} \\ \text{CH}_3 \end{matrix} \text{CH} - \text{CH} \begin{matrix} \text{COO}^- \\ \\ \text{N}^+ \text{H}_3 \end{matrix}$	Threonine Thr T MW = 119
Isoleucine Ile I MW = 131	$\begin{matrix} ^- \text{OOC} \\ \\ \text{H}_3\text{N}^+ \end{matrix} \text{CH} - \text{CH} \begin{matrix} \text{CH}_3 \\ \\ \text{CH}_2 - \text{CH}_3 \end{matrix}$	$\text{HS} - \text{CH}_2 - \text{CH} \begin{matrix} \text{COO}^- \\ \\ \text{N}^+ \text{H}_3 \end{matrix}$	Cysteine Cys C MW = 121
Phenylalanine Phe F MW = 131	$\begin{matrix} ^- \text{OOC} \\ \\ \text{H}_3\text{N}^+ \end{matrix} \text{CH} - \text{CH}_2 - \text{C}_6\text{H}_5$	$\text{HO} - \text{C}_6\text{H}_4 - \text{CH}_2 - \text{CH} \begin{matrix} \text{COO}^- \\ \\ \text{N}^+ \text{H}_3 \end{matrix}$	Tyrosine Tyr Y MW = 181
Tryptophan Trp W MW = 204	$\begin{matrix} ^- \text{OOC} \\ \\ \text{H}_3\text{N}^+ \end{matrix} \text{CH} - \text{CH}_2 - \text{C}_8\text{H}_6\text{N}_2$	$\text{NH}_2 \begin{matrix} \\ \text{C} \\ \\ \text{O} \end{matrix} - \text{CH}_2 - \text{CH} \begin{matrix} \text{COO}^- \\ \\ \text{N}^+ \text{H}_3 \end{matrix}$	Asparagine Asn N MW = 132
Methionine Met M MW = 149	$\begin{matrix} ^- \text{OOC} \\ \\ \text{H}_3\text{N}^+ \end{matrix} \text{CH} - \text{CH}_2 - \text{CH}_2 - \text{S} - \text{CH}_3$	$\text{NH}_2 \begin{matrix} \\ \text{C} \\ \\ \text{O} \end{matrix} - \text{CH}_2 - \text{CH}_2 - \text{CH} \begin{matrix} \text{COO}^- \\ \\ \text{N}^+ \text{H}_3 \end{matrix}$	Glutamine Gln Q MW = 146
Proline Pro P MW = 115	$\begin{matrix} ^- \text{OOC} \\ \\ \text{CH} \\ \\ \text{HN} \\ \\ \text{CH}_2 \end{matrix} - \text{CH}_2 - \text{CH}_2$	POLAR BASIC $\text{NH}_3^+ - \text{CH}_2 - (\text{CH}_2)_3 - \text{CH} \begin{matrix} \text{COO}^- \\ \\ \text{N}^+ \text{H}_3 \end{matrix}$	Lysine Lys K MW = 146
Aspartic acid Asp D MW = 133	POLAR ACIDIC $\begin{matrix} ^- \text{OOC} \\ \\ \text{H}_3\text{N}^+ \end{matrix} \text{CH} - \text{CH}_2 - \text{C}(=\text{O})\text{O}^-$	$\text{NH}_2 \begin{matrix} \\ \text{C} \\ \\ \text{N}^+ \text{H}_2 \end{matrix} - \text{NH} - (\text{CH}_2)_3 - \text{CH} \begin{matrix} \text{COO}^- \\ \\ \text{N}^+ \text{H}_3 \end{matrix}$	Arginine Arg R MW = 174
Glutamine acid Glu E MW = 147	$\begin{matrix} ^- \text{OOC} \\ \\ \text{H}_3\text{N}^+ \end{matrix} \text{CH} - \text{CH}_2 - \text{CH}_2 - \text{C}(=\text{O})\text{O}^-$	$\text{HN} \begin{matrix} \\ \text{C} \\ \\ \text{NH} \end{matrix} - \text{CH}_2 - \text{CH} \begin{matrix} \text{COO}^- \\ \\ \text{N}^+ \text{H}_3 \end{matrix}$	Histidine His H MW = 155

Amino acids can be classified by R group

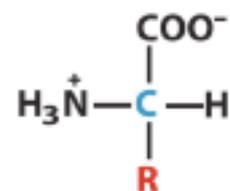


TABLE 3-1 Properties and Conventions Associated with the Common Amino Acids Found in Proteins

Amino acid	Abbreviation/ symbol	M_r	pK_a values			pI	Hydropathy index*	Occurrence in proteins (%) [†]
			pK_1 (—COOH)	pK_2 (—NH ₃ ⁺)	pK_R (R group)			
Nonpolar, aliphatic								
R groups								
Glycine	Gly G	75	2.34	9.60		5.97	-0.4	7.2
Alanine	Ala A	89	2.34	9.69		6.01	1.8	7.8
Proline	Pro P	115	1.99	10.96		6.48	1.6	5.2
Valine	Val V	117	2.32	9.62		5.97	4.2	6.6
Leucine	Leu L	131	2.36	9.60		5.98	3.8	9.1
Isoleucine	Ile I	131	2.36	9.68		6.02	4.5	5.3
Methionine	Met M	149	2.28	9.21		5.74	1.9	2.3
Aromatic R groups								
Phenylalanine	Phe F	165	1.83	9.13		5.48	2.8	3.9
Tyrosine	Tyr Y	181	2.20	9.11	10.07	5.66	-1.3	3.2
Tryptophan	Trp W	204	2.38	9.39		5.89	-0.9	1.4

*A scale combining hydrophobicity and hydrophilicity of R groups; it can be used to measure the tendency of an amino acid to seek an aqueous environment (— values) or a hydrophobic environment (+ values). See Chapter 11. From Kyte, J. & Doolittle, R.F. (1982) A simple method for displaying the hydropathic character of a protein. *J. Mol. Biol.* **157**, 105-132.

[†]Average occurrence in more than 1,150 proteins. From Doolittle, R.F. (1989) Redundancies in protein sequences. In *Prediction of Protein Structure and the Principles of Protein Conformation* (Fasman, G.D., ed.), pp. 599-623, Plenum Press, New York.

Amino acids can be classified by R group

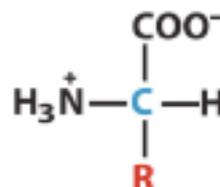


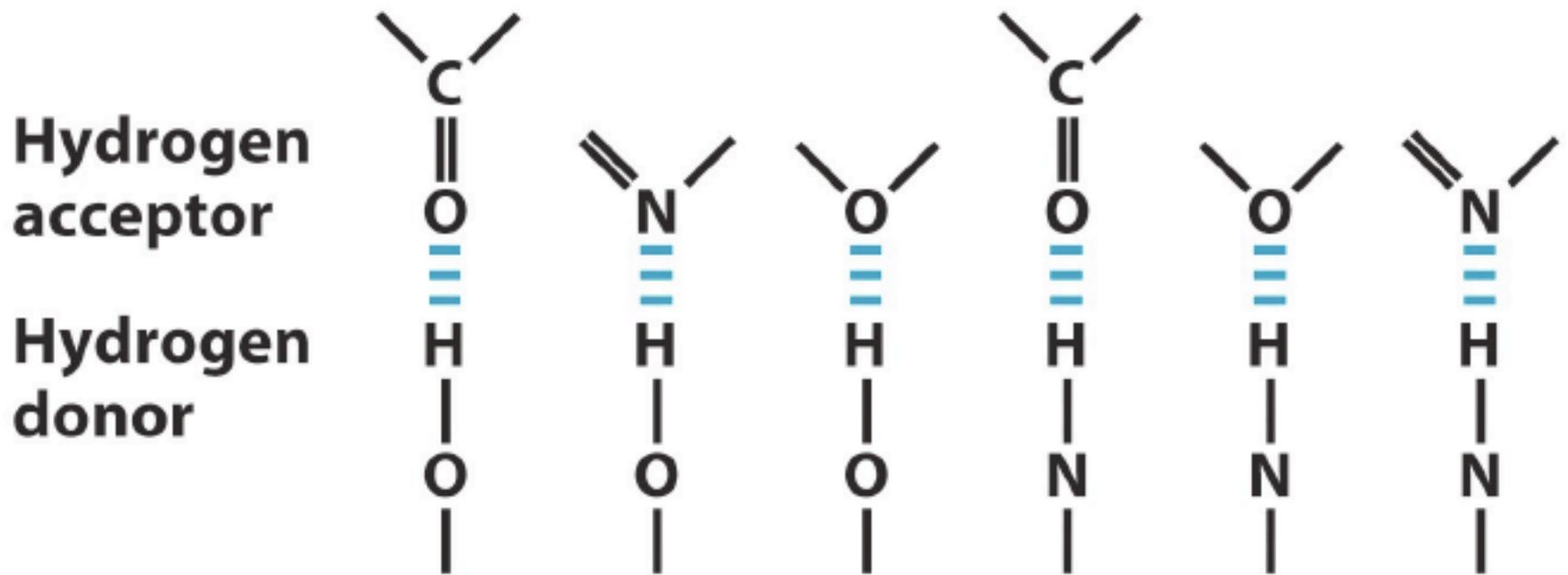
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			pK_1 (—COOH)	pK_2 (—NH ₃ ⁺)	pK_R (R group)			
Polar, uncharged								
R groups								
Serine	Ser S	105	2.21	9.15		5.68	-0.8	6.8
Threonine	Thr T	119	2.11	9.62		5.87	-0.7	5.9
Cysteine	Cys C	121	1.96	10.28	8.18	5.07	2.5	1.9
Asparagine	Asn N	132	2.02	8.80		5.41	-3.5	4.3
Glutamine	Gln Q	146	2.17	9.13		5.65	-3.5	4.2
Positively charged								
R groups								
Lysine	Lys K	146	2.18	8.95	10.53	9.74	-3.9	5.9
Histidine	His H	155	1.82	9.17	6.00	7.59	-3.2	2.3
Arginine	Arg R	174	2.17	9.04	12.48	10.76	-4.5	5.1
Negatively charged								
R groups								
Aspartate	Asp D	133	1.88	9.60	3.65	2.77	-3.5	5.3
Glutamate	Glu E	147	2.19	9.67	4.25	3.22	-3.5	6.3

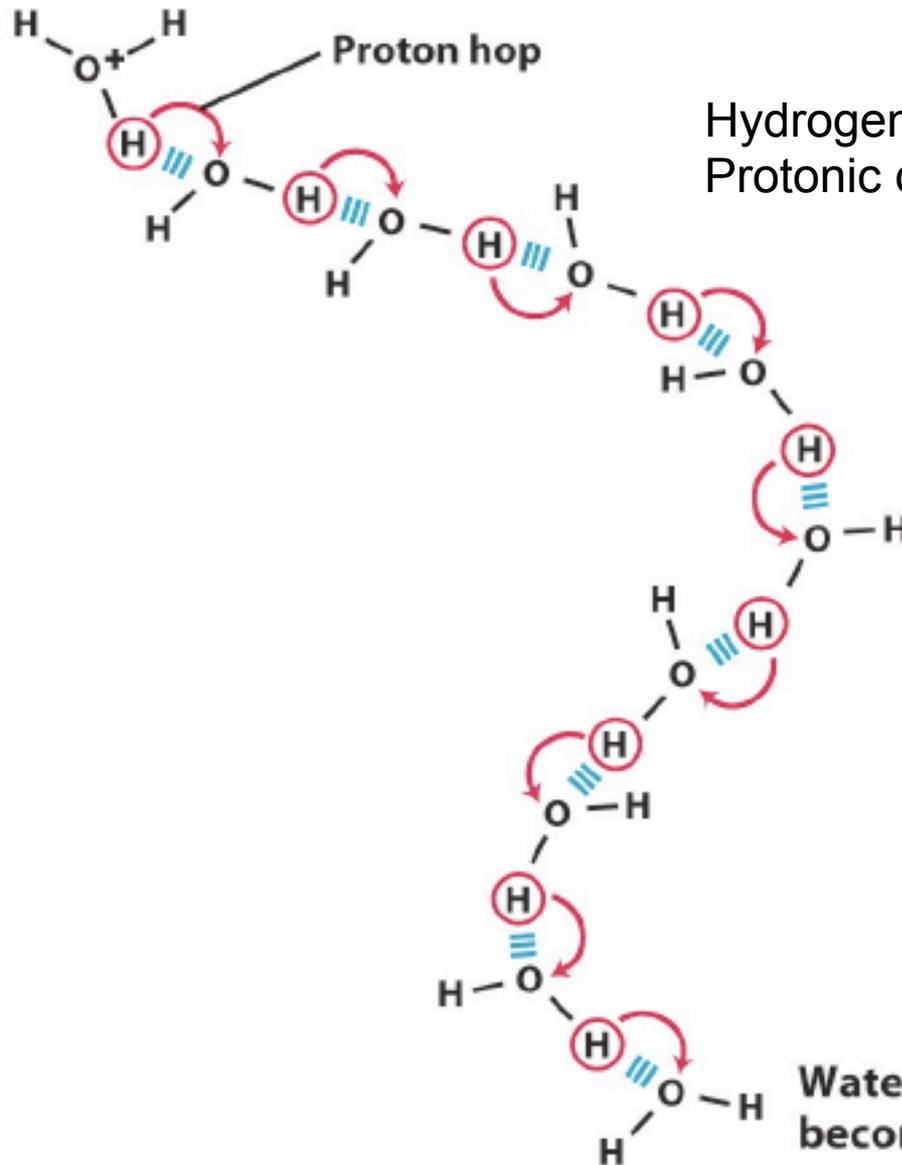
*A scale combining hydrophobicity and hydrophilicity of R groups; it can be used to measure the tendency of an amino acid to seek an aqueous environment (- values) or a hydrophobic environment (+ values). See Chapter 11. From Kyte, J. & Doolittle, R.F. (1982) A simple method for displaying the hydropathic character of a protein. *J. Mol. Biol.* **157**, 105-132.

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Hydrogen bonds occur in water and between biomolecules



Hydronium ion gives up a proton

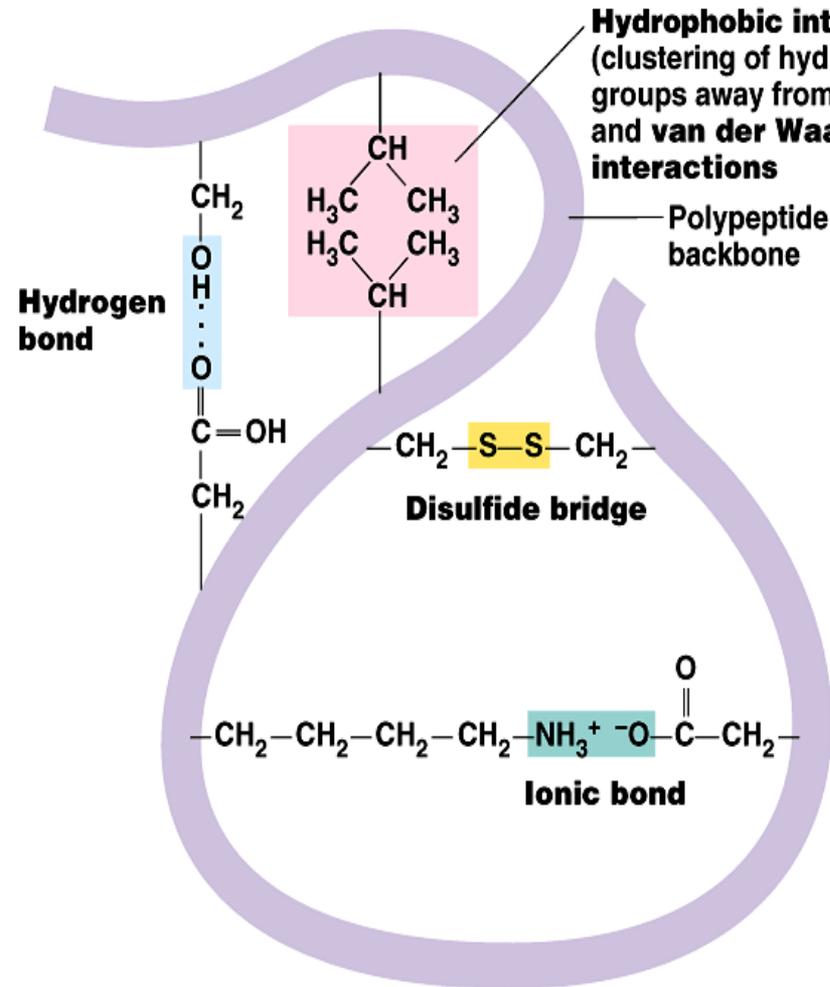


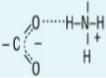
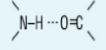
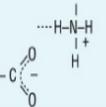
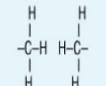
Hydrogen bonds networks...
Protonic currents, quantum effects

Water accepts proton and becomes a hydronium ion

Internal Protein Interactions

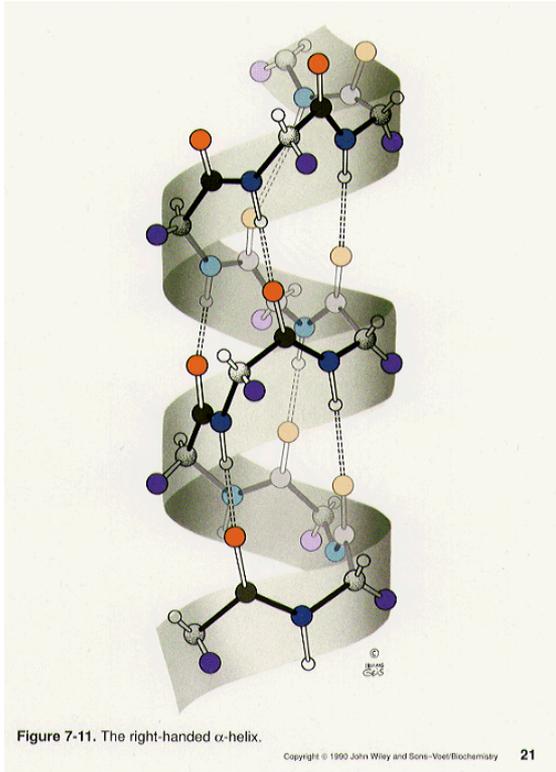
- The thermal stability of a protein is about 60 kJ/mol



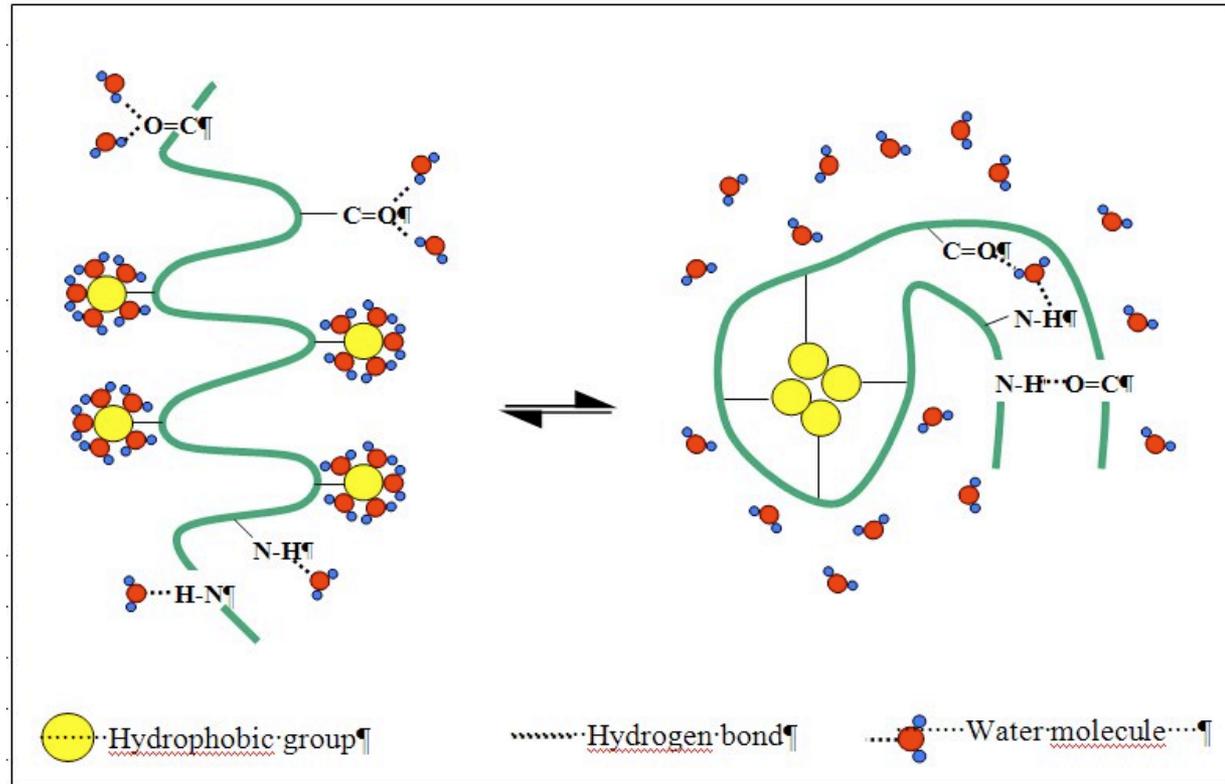
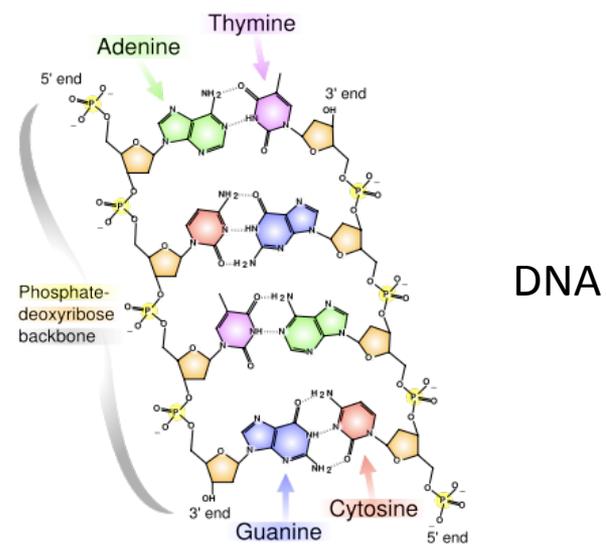
Interaction	Example	Distance dependence	Typical distance	Free energy (bond dissociation enthalpies for the covalent bonds)
Covalent bond	$-C_{\alpha}-C-$	-	1.5 Å	356 kJ/mole (610 kJ/mole for a C=C bond)
Disulfide bond	$-Cys-S-S-Cys-$	-	2.2 Å	167 kJ/mole
Salt bridge		Donor (here N), and acceptor (here O) atoms <3.5 Å	2.8 Å	12.5–17 kJ/mole; may be as high as 30 kJ/mole for fully or partially buried salt bridges (see text), less if the salt bridge is external
Hydrogen bond		Donor (here N), and acceptor (here O) atoms <3.5 Å	3.0 Å	2–6 kJ/mole in water; 12.5–21 kJ/mole if either donor or acceptor is charged
Long-range electrostatic interaction		Depends on dielectric constant of medium. Screened by water. $1/r$ dependence	Variable	Depends on distance and environment. Can be very strong in nonpolar region but very weak in water
Van der Waals interaction		Short range. Falls off rapidly beyond 4 Å separation. $1/r^6$ dependence	3.5 Å	4 kJ/mole (4–17 in protein interior) depending on the size of the group (for comparison, the average thermal energy of molecules at room temperature is 2.5 kJ/mole)

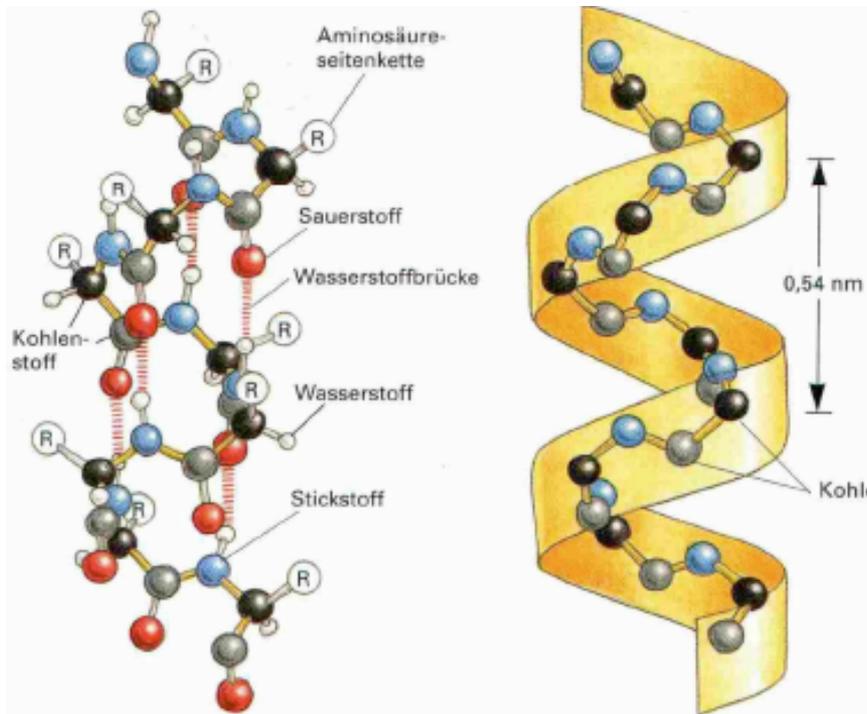
- Cooperative interactions: one bond favors the formation of another bond etc..

Hydrogen-BONDS

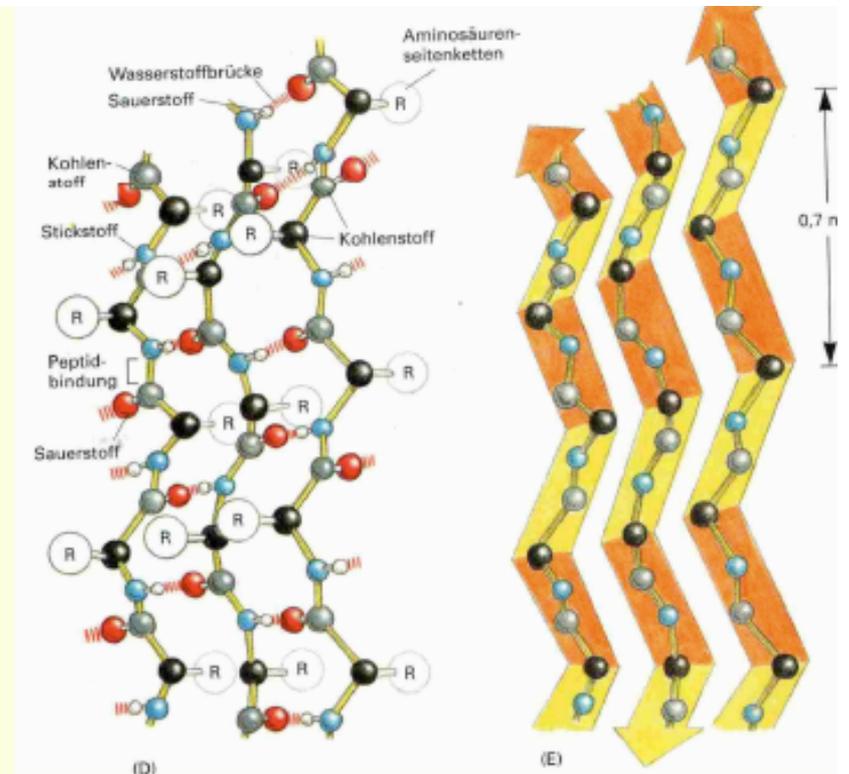


Proteins





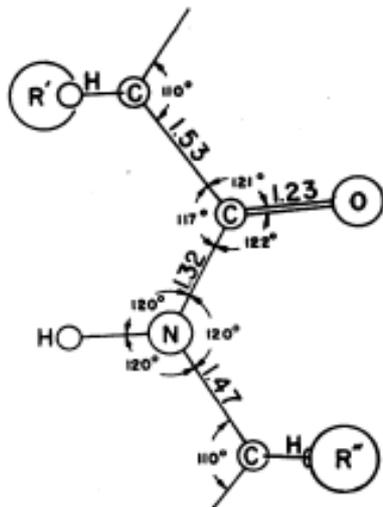
α -helix



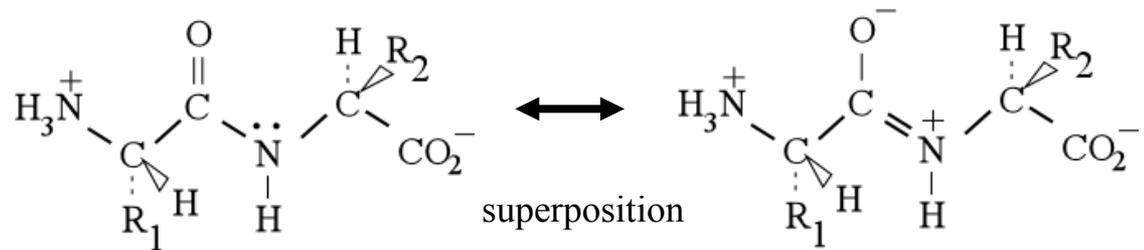
β -sheet

Pauling and Corey (1951) predicted that amino acid sequences could form regular geometric shapes via hydrogen bonding.

Determinants of helical structure



Distances and angles
Between atoms

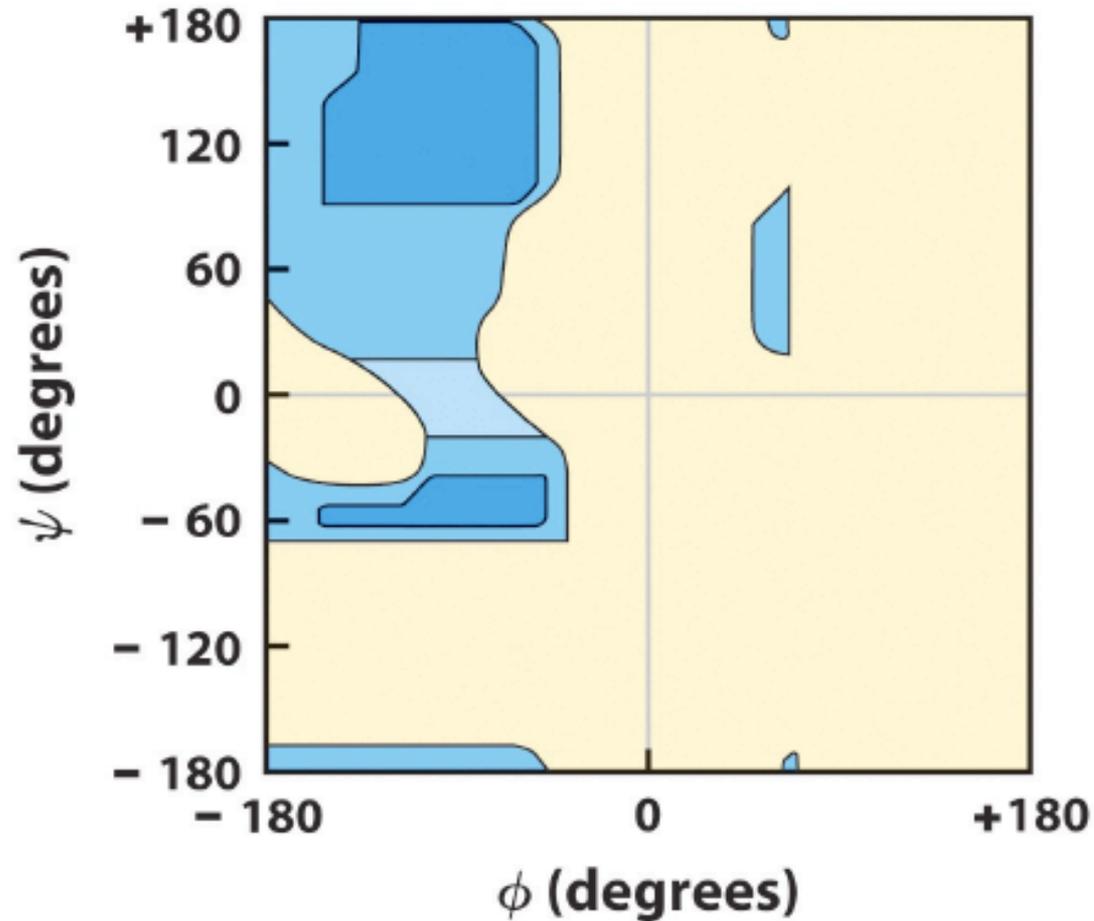


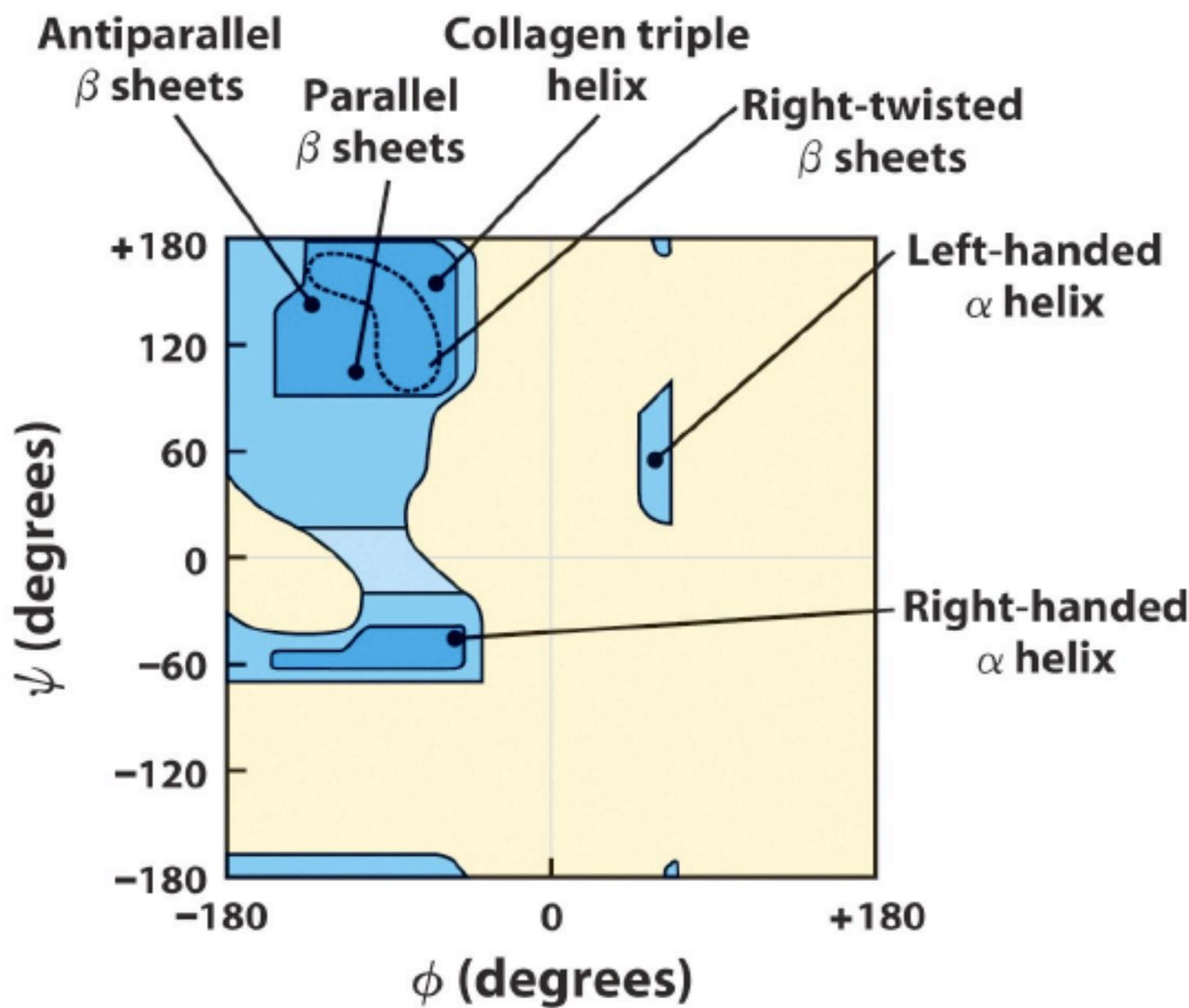
Resonant partial double bond character
of peptide bond induces planar
arrangement of atoms



All hydrogen bonds should be satisfied,
i.e. distance N-O of about 2.7Å and angle
between C = O and H - N less than $\sim 30^\circ$

Ramachandran plot





Structural Domains

- independent functional subproteins: thermal stability, correlated dynamics
- Example: Pawson's domains



The genetic code: codons code for amino acids

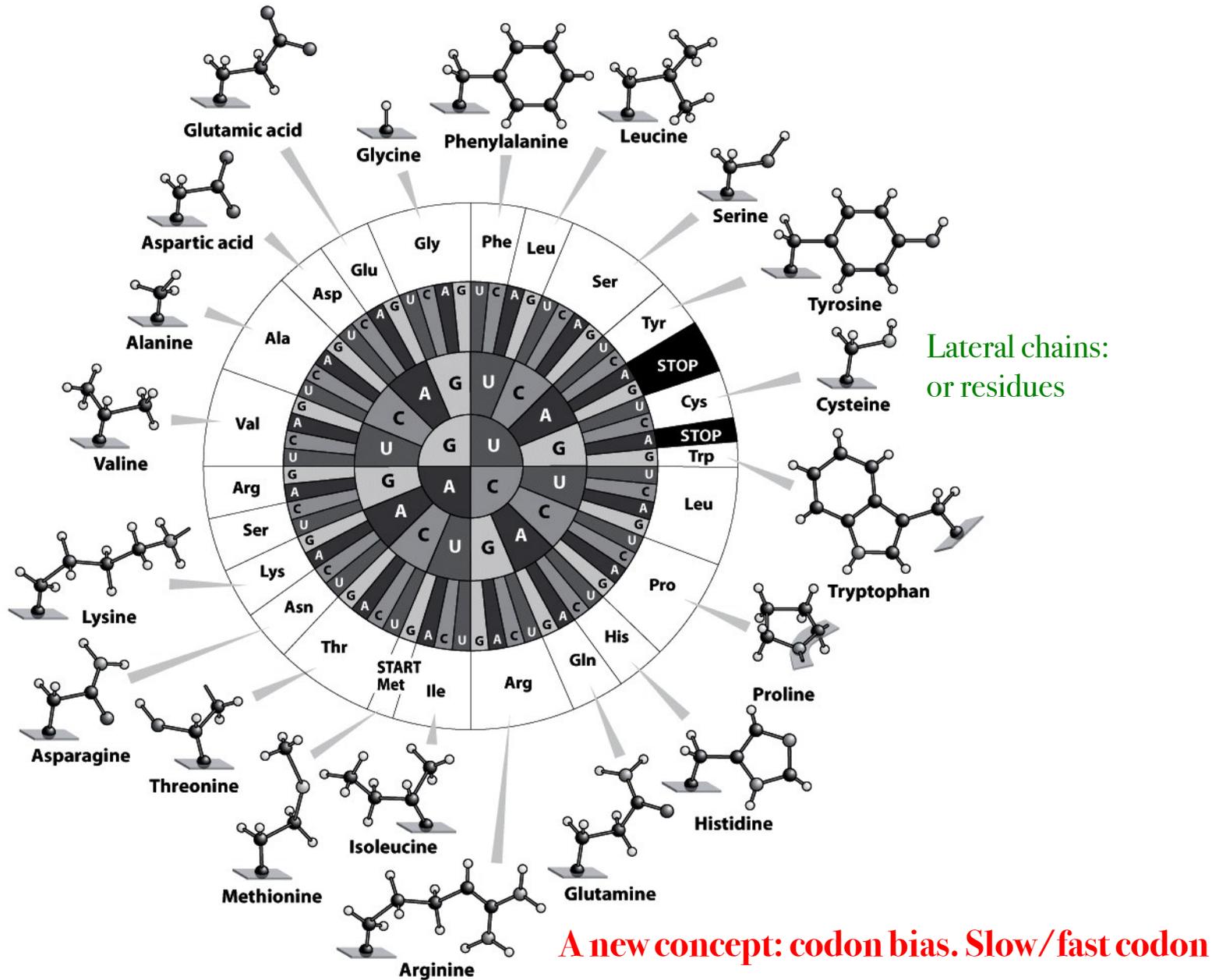
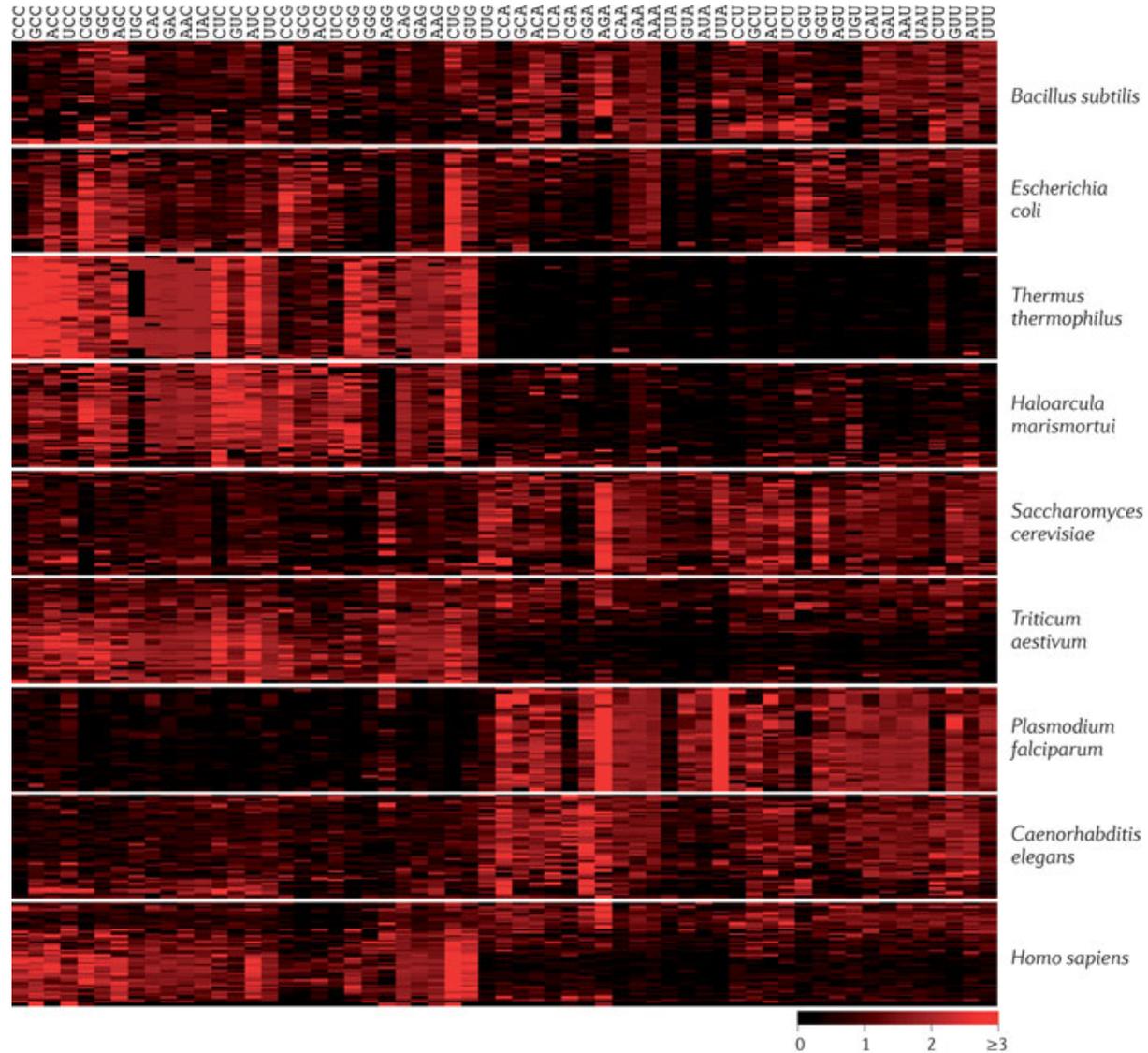


Figure 1.4 Physical Biology of the Cell (© Garland Science 2009)

Possible mechanisms of translational regulation

- optimality of ribosomal attachment site
- mRNA secondary structure
- codon usage
- t-RNA BIOLOGY

The codon bias in genomes



The same protein can be encoded in many ways...

amino acid sequence: M**P**KSNFRFGE

relative
concentration
of tRNA in
the cell



The effect of (or on?) GC content

Mutation pressure

Selection

Amino acid composition

Nucleotide composition

Inter-genic composition (esp in bacteria) explain codon bias

Codon bias

Coding

Inter-genic

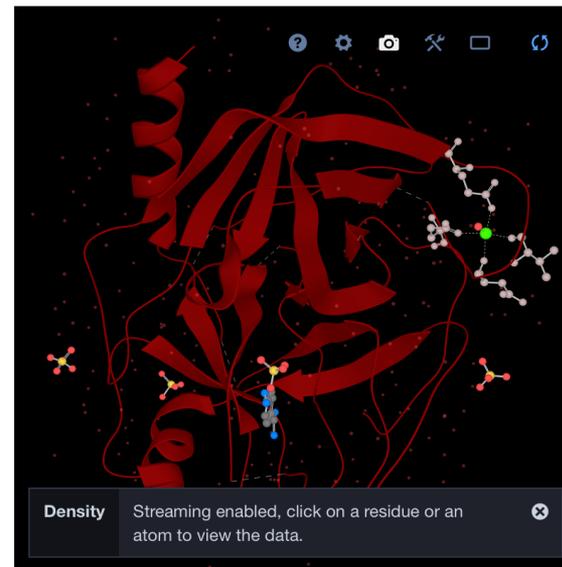
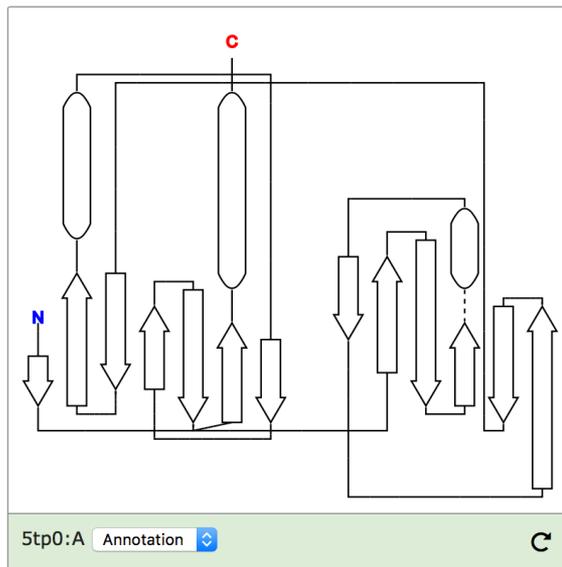
Coding

Tutorial

FASTA Sequence

```
>pdb | 5tp0 | A
```

```
IVGGYTCEENSLPYQVSLNSGSHFCGGSLISEQWVVSAAHCYKTRIQVRLGEHNIKVLEGNEQFINAA  
KIIIRHPKYNRDTLDNDIMLIKLS SPAVINARVSTISLPTAPPAAGTECLISGWGNTLSFGADYPDELK  
CLDAPVLTQAECKASYPGKITNSMFCVGFLEGGKDSCQRDSGGPVVCNGQLQGVVSWGHC A WKNRPG  
VYTKVYNYVDWIKDTIAANS
```



Coordinate systems

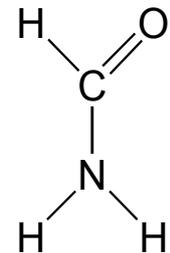
At least two ways of specifying atomic coordinates:

Cartesian coordinates from the Protein Data Bank .pdb files.

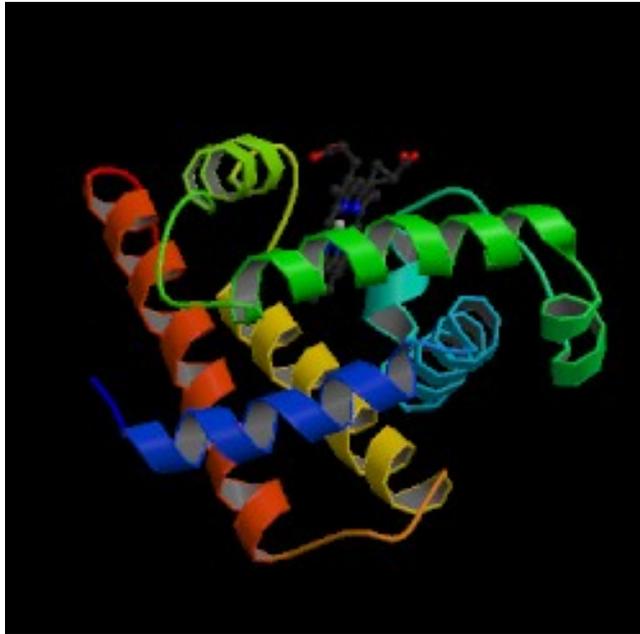
X,Y,Z with respect to a laboratory system, modulo a RQTO-TRANSLATION

N atoms \times 3N cartesian coordinates

```
REMARK      4
REMARK      4 FORM COMPLIES WITH FORMAT V. 2.0, 26-MAR-2003
ATOM         1  C1  ALHD      1      3.450  0.774 -9.239  1.00  0.00
ATOM         2  O2  ALHD      1      4.639  0.791 -8.925  1.00  0.00
ATOM         3  H1  ALHD      1      2.972 -0.166 -9.513  1.00  0.00
ATOM         4  N1  AMDE     1B      2.756  1.892 -9.246  1.00  0.00
ATOM         5 1H1  AMDE     1B      1.760  1.878 -9.510  1.00  0.00
ATOM         6 2H1  AMDE     1B      3.207  2.781 -8.987  1.00  0.00
END
```



Proof came 7 years later...



John Cowdery Kendrew
The Nobel Prize in Chemistry 1962

Kendrew, J. C., Bodo, G., Dintzis, H. M. Parrish, R. G., Wyckoff, H., and Phillips, D. C. **A Three-Dimensional Model of the Myoglobin Molecule Obtained by X-ray Analysis.** *Nature*, 181, 662 (1958).

Pauling and Corey papers series – PNAS April 1951

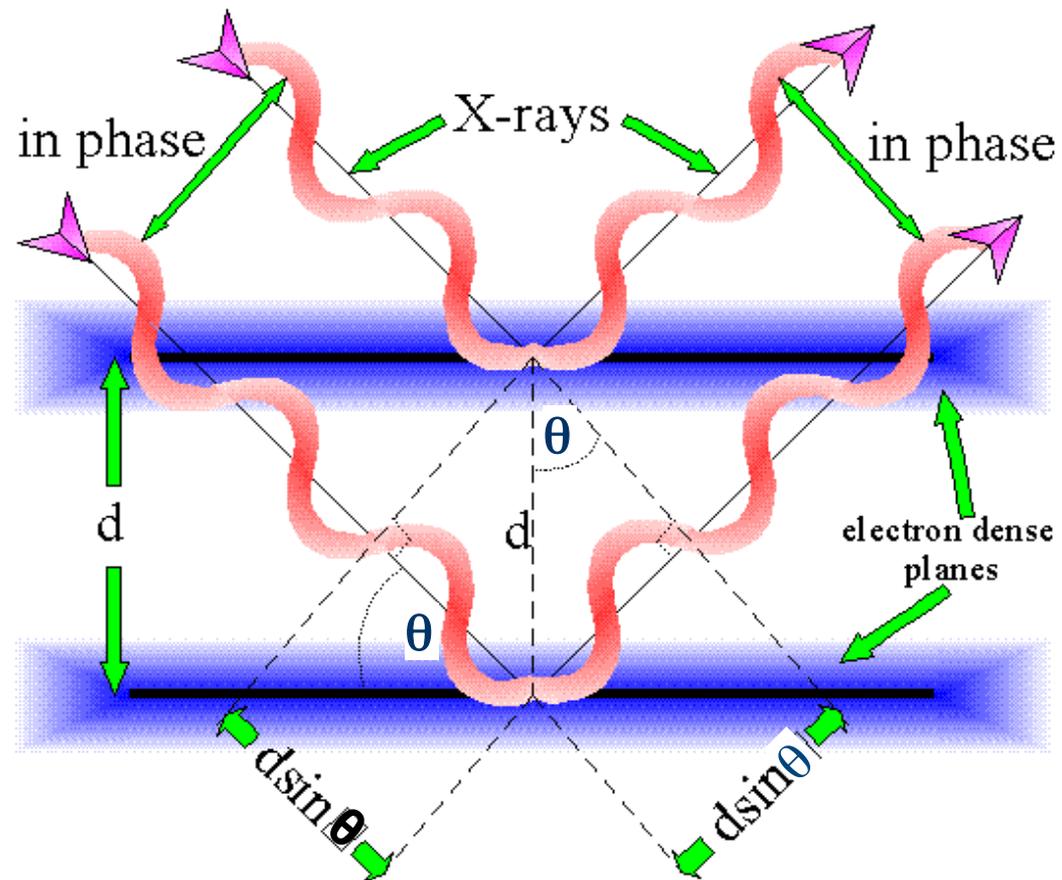
1. Pauling, L., Corey, R.B. and Branson H. R. **The Structure of Proteins: Two Hydrogen-Bonded Helical Configurations of the Polypeptide Chain.** PNAS, **37**, 205-211, (1951).
2. Pauling, L. & Corey, R. B. **Atomic Coordinates and Structure Factors for Two Helical Configurations of Polypeptide Chains.** PNAS, **37**, 235-240, (1951).
3. Pauling, L. & Corey, R. B. **The Structure of Synthetic Polypeptides.** PNAS, **37**, 241-250, (1951).
4. Pauling, L. & Corey, R. B. **The Pleated Sheet, A New Layer Configuration of Polypeptide Chains.** PNAS, **37**, 251-256, (1951).
5. Pauling, L. & Corey, R. B. **The Structure of Feather Rachis Keratin.** PNAS, **37**, 256-261, (1951).
6. Pauling, L. & Corey, R. B. **The Structure of Hair, Muscle, and Related Proteins.** PNAS, **37**, 261-271, (1951).
7. Pauling, L. & Corey, R. B. **The Structure of Fibrous Proteins of the Collagen-Gelatin Group.** PNAS, **37**, 272-281, (1951).
8. Pauling, L. & Corey, R. B. **The Polypeptide-Chain Configuration in Hemoglobin and Other Globular Proteins.** PNAS, **37**, 282-285, (1951).

X-Rays crystallography – the tool of structural biology

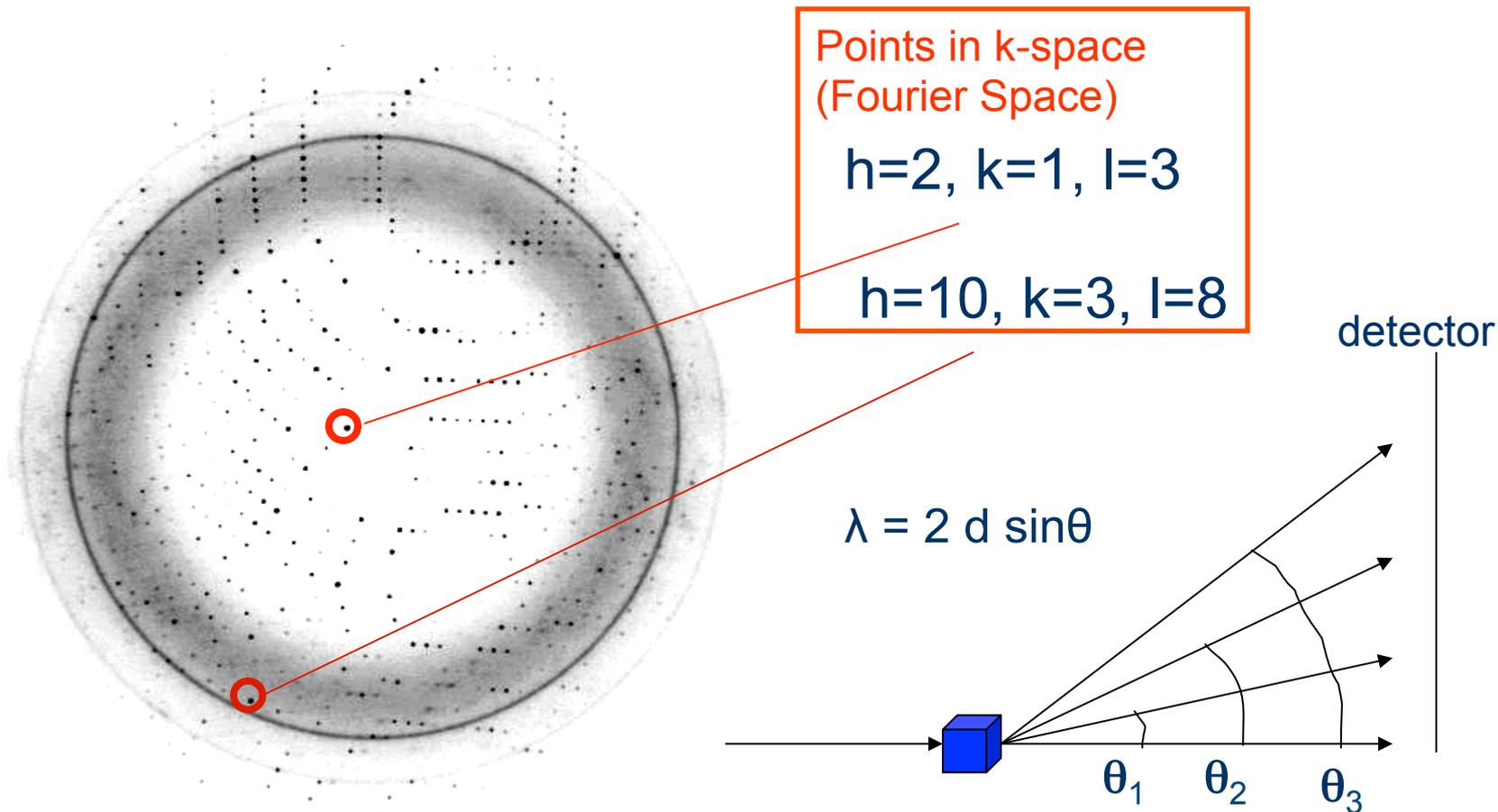
- X-ray are (weakly) scattered by electrons
- Diffraction from a single molecule is weak so use a crystal
- Why X-ray?
Wavelength of visible light: ~ 500 nm
Bond lengths in proteins: ~ 0.15 nm
Typical X-ray wavelength: ~ 0.15 nm
- + Multiple copies of the molecule increases diffraction
- - Crystalline structure imposes constraints on diffraction pattern
- OTHER TECHNIQUES: **NMR, CRYO ELECTRON MICROSCOPY**

Diffraction occurs at particular angles

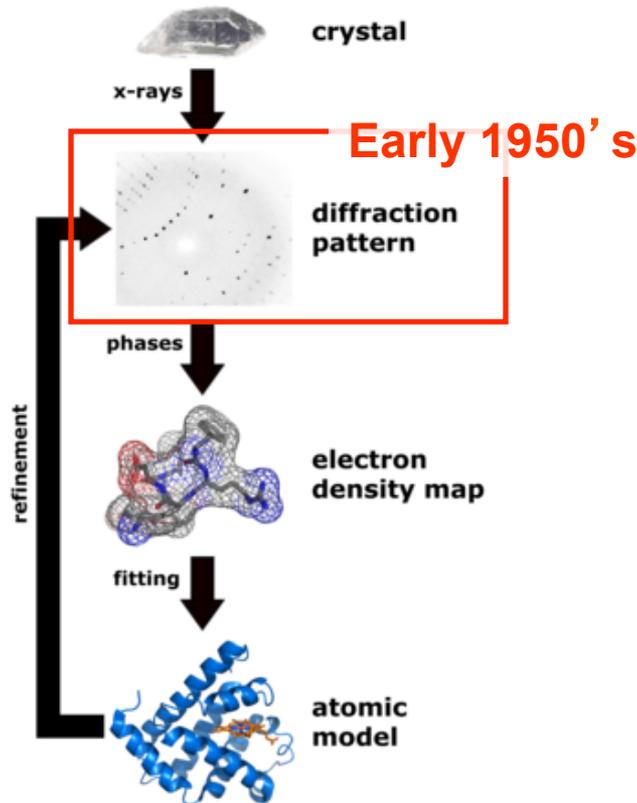
- Diffraction spots are the result of constructive interference from multiple scatterers satisfying Bragg's Law:
 $\lambda = 2 d \sin\theta$



Each Spot Represents a Unique Set of Bragg Planes



Modern X-Ray Crystallography



Need good crystals for better resolution, which is difficult in proteins (need right conditions) and sometimes nearly impossible (e.g. membranal proteins)

High resolution details are faint – requires good experimental apparatus

Recorded intensity give only the magnitude but not the phase of the complex “form factor”

Error in density map lead to un-realistic atom assignment, requiring iterative refinement process

The Protein Data Bank (www.pdb.org)

The screenshot shows the RCSB Protein Data Bank website as it appeared in late 2006. The browser window title is "RCSB Protein Data Bank - Microsoft Internet Explorer". The address bar shows the URL "http://www.pdb.org/pdb/home/home.do". The website header includes the RCSB PDB logo and the text "A MEMBER OF THE PDB". Below the logo, it states "An Information Portal to Biological Macromolecular Structures" and "As of Tuesday Dec 19, 2006 there are 40749 Structures". A search bar is located below the header, with options for "PDB ID or keyword" and "Author".

The main content area is titled "Welcome to the RCSB PDB". It contains several paragraphs of text:

- The first paragraph states: "The RCSB PDB provides a variety of tools and resources for studying the structures of biological macromolecules and their relationships to sequence, function, and disease."
- The second paragraph states: "The RCSB is a member of the wwPDB whose mission is to ensure that the PDB archive remains an international resource with uniform data."
- The third paragraph states: "This site offers tools for browsing, searching, and reporting that utilize the data resulting from ongoing efforts to create a more consistent and comprehensive archive."
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- The fifth paragraph states: "A [narrated tutorial](#) illustrates how to search, navigate, browse, generate reports and visualize structures using this new site. [This requires the Macromedia [Flash player download](#).]"

On the left side, there is a navigation menu with the following items:

- Home
- Tutorial About This Site
- Getting Started
- Download Files
- Deposit and Validate
- Structural Genomics
- Dictionaries & File Formats
- Software Tools
- General Education
- BioSync
- General Information
- Acknowledgements
- Frequently Asked Questions
- Known Problems
- Report Bugs/Comments

On the right side, there is a "NEWS" section with the following items:

- Complete News
- Newsletter
- Discussion Forum

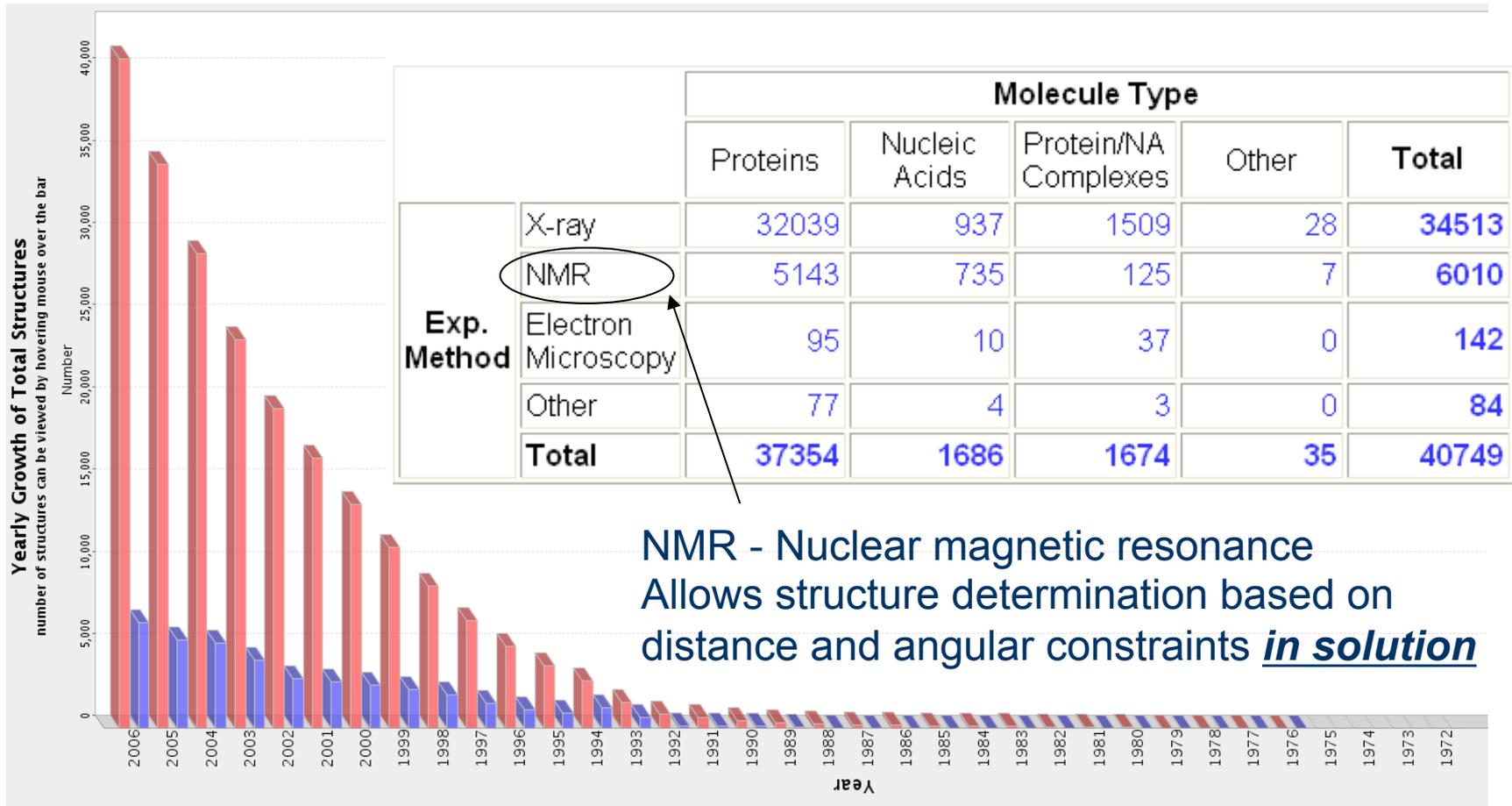
Below the news items, there is a date "19-December-2006" and a headline "RCSB PDB Poster Prize Awarded at AsCA". The text below the headline reads: "Thanks to everyone who participated in the recent competition for best student poster related to macromolecular crystallography at the Joint Conference of the Asian Crystallographic Association and the Crystallographic Society of Japan (AsCA; November 20-23 in Tsukuba, Japan)."

At the bottom of the page, there is a section titled "Molecule of the Month: Transposase". It features a 3D molecular model of a transposase and the text: "In the 1940's, Barbara McClintock discovered that...".

The Windows taskbar at the bottom shows the start button, several open applications, and the system tray with the time "3:05 PM".

The PDB contains over 40,000 structures (as of December 2006)

RECENTLY CRYO_EM JOINED!



PDB Current Holdings Breakdown

Exp.Method	Proteins	Nucleic Acids	Protein/NA Complexes	Other	Total
X-RAY	108448	1826	5512	4	115
NMR	10341	1200	241	8	11
ELECTRON MICROSCOPY	1061	30	380	0	1
HYBRID	99	3	2	1	
other	188	4	6	13	
Total	120137	3063	6141	26	129

(Click on any number to retrieve the results from that category.)

105563 structures in the PDB have a structure factor file.

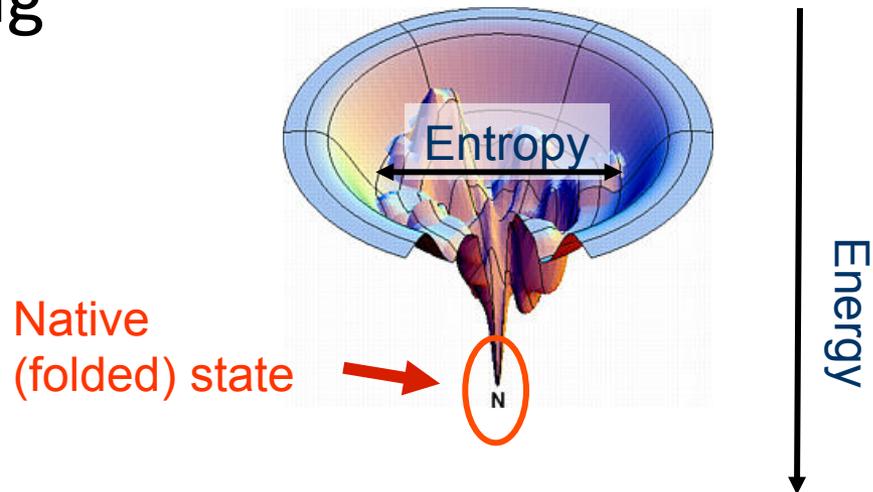
9124 structures in the PDB have an NMR restraint file.

2882 structures in the PDB have a chemical shifts file.

1466 structures in the PDB have a 3DEM map file.

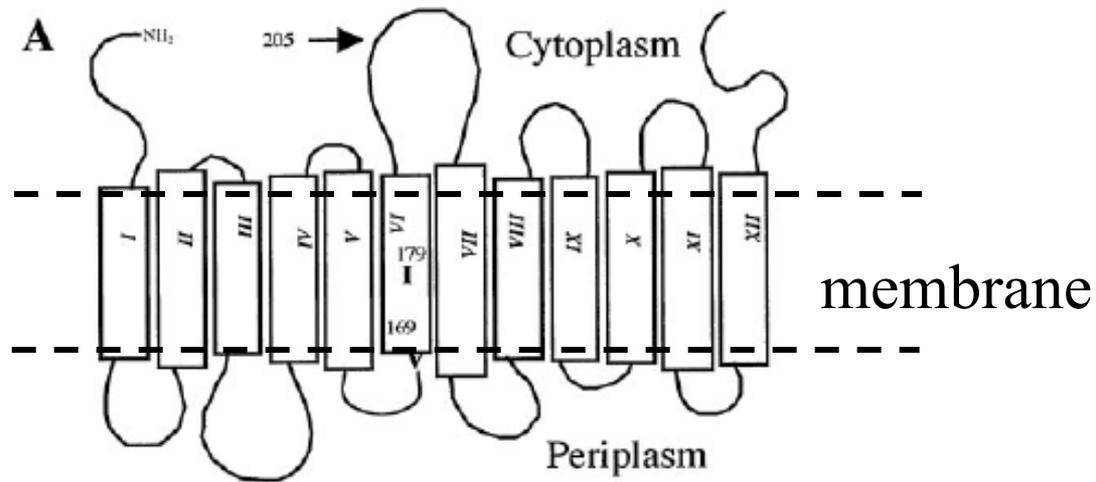
The Protein folding problem...

- Late **1980's** - Wolynes et al. present the “Energy Landscape” or “Folding Funnel” model for protein folding



- **2006** – There is still no precise understanding how proteins fold fast (up to $\mu\text{sec!}$), reliably and accurately to their native structure

Alpha-helices appear a lot in trans-membranal proteins



1pv6.pdb

E.g. Lactose permease (LacY)

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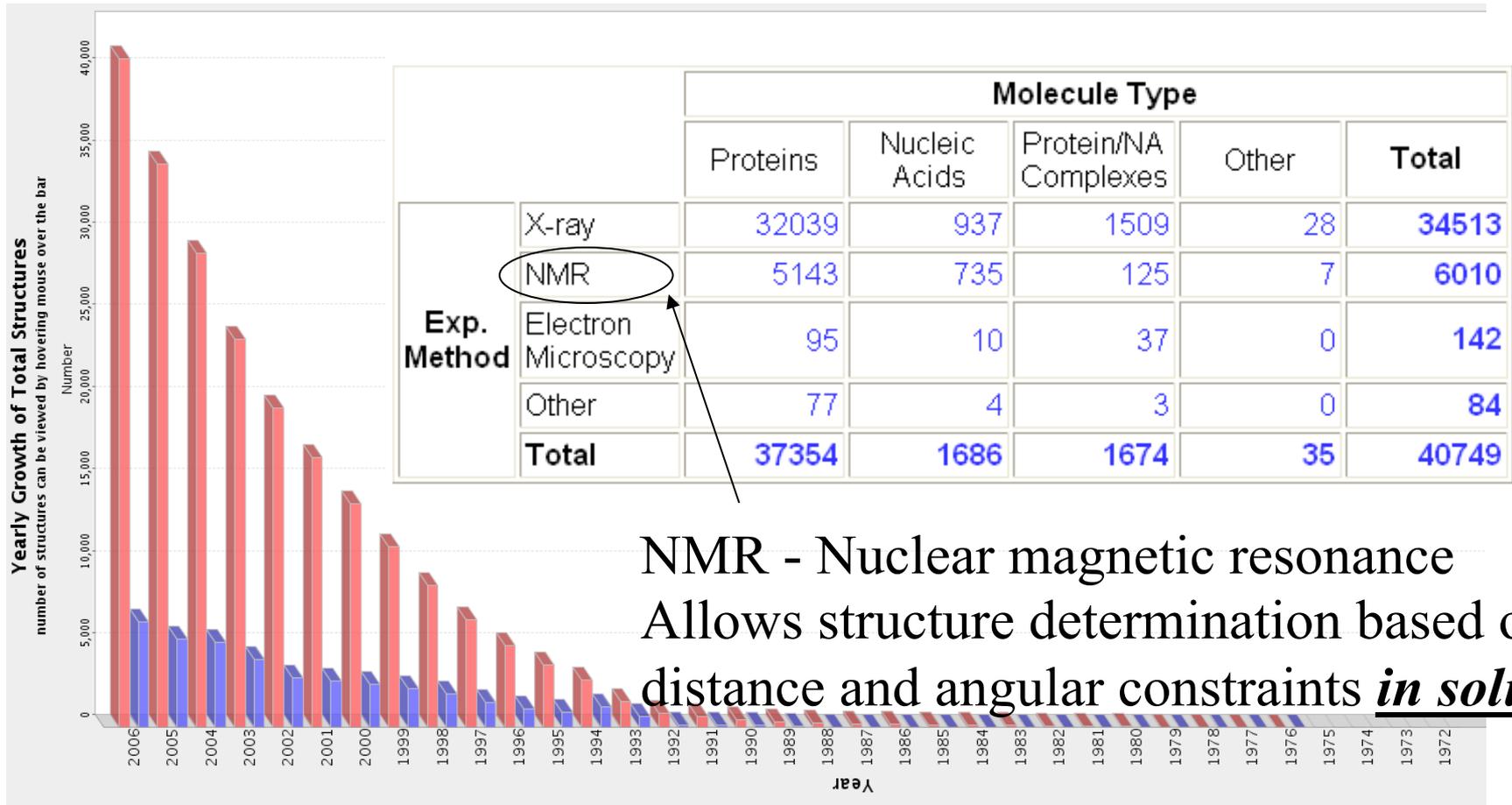
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NMR - Nuclear magnetic resonance
Allows structure determination based on
distance and angular constraints *in solution*