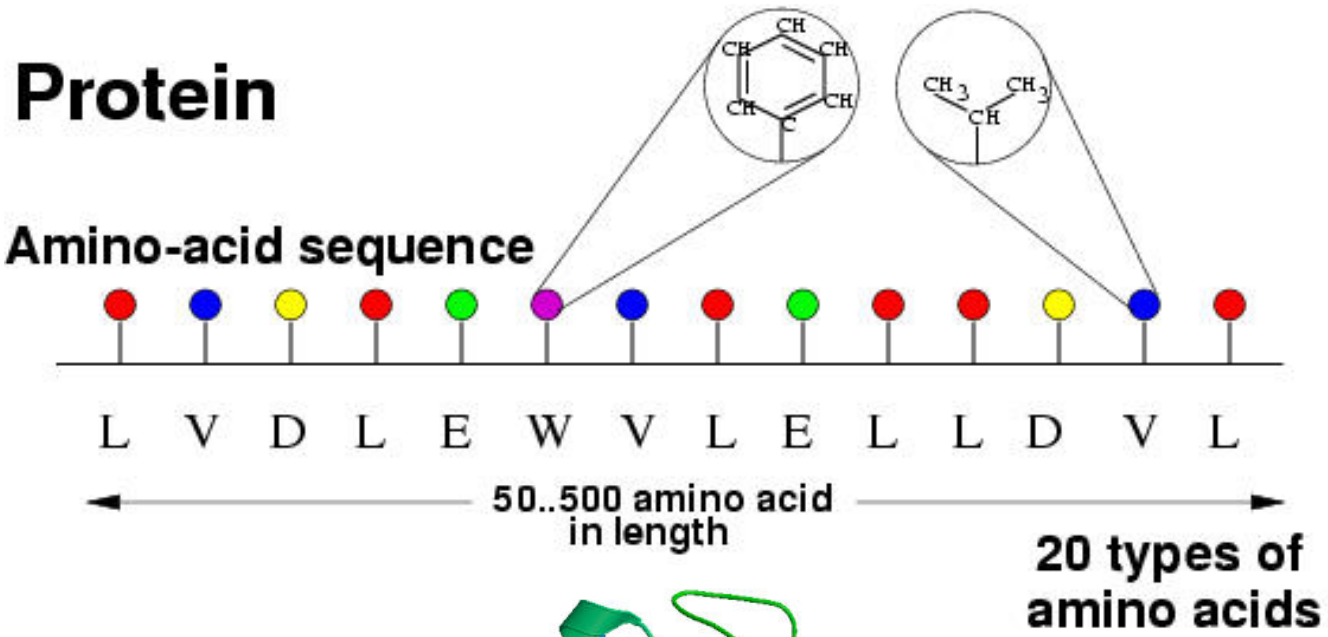
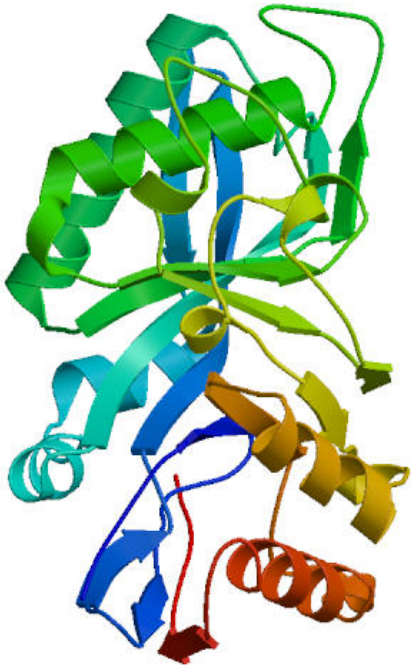
Outline

1. Amino acids
2. Forces
3. Protein structure
4. Sequence-structure mapping

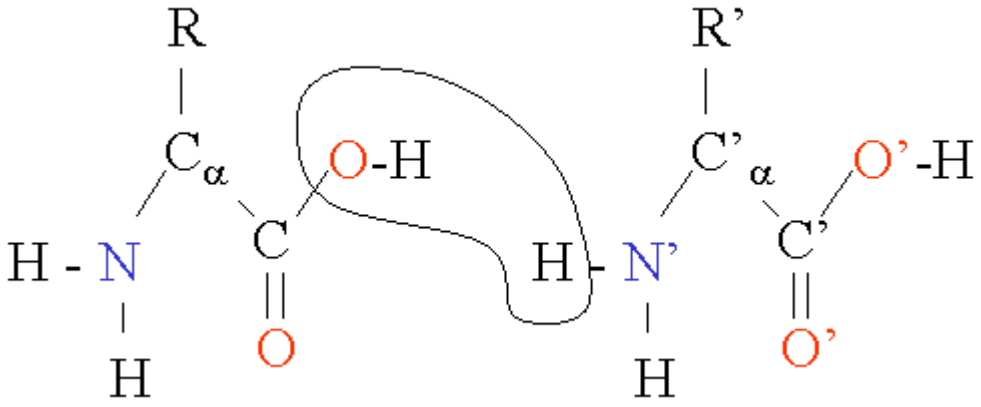
Proteins

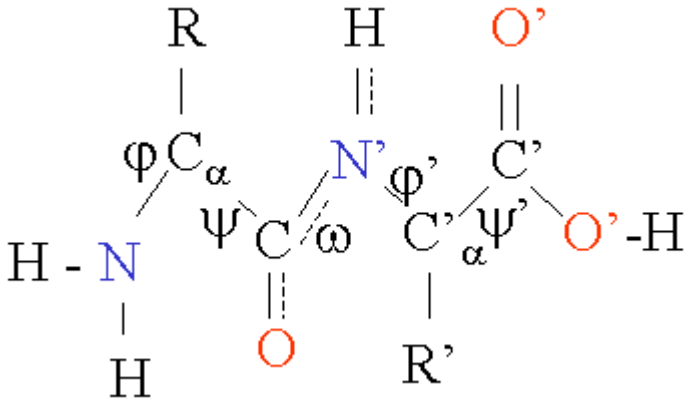


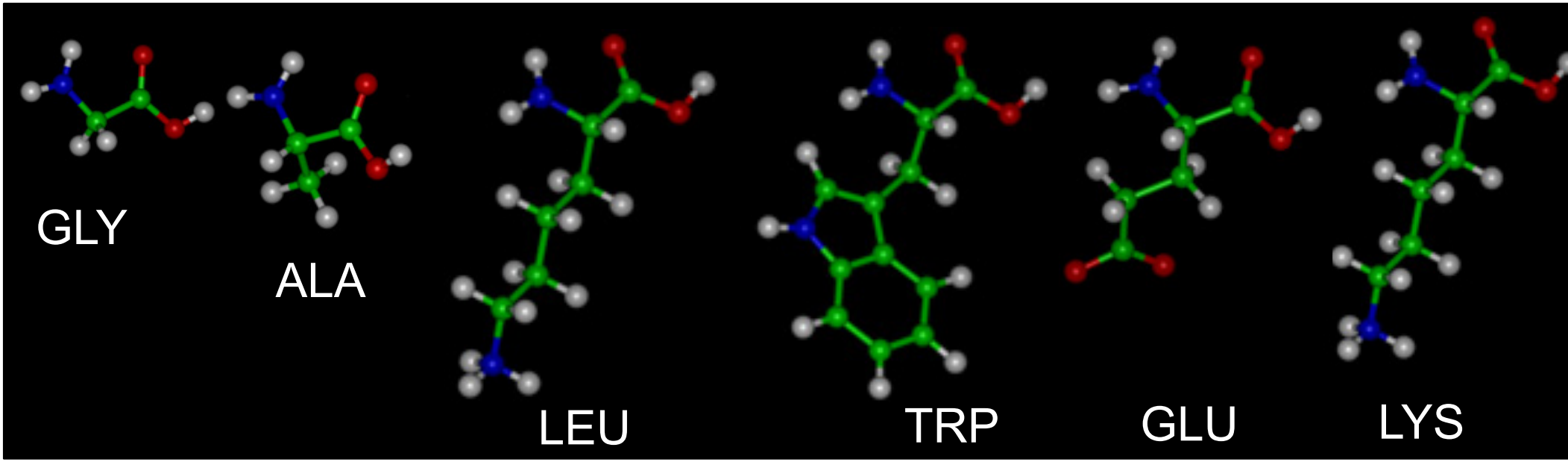
Structure



Amino Acids







Hydrophobic

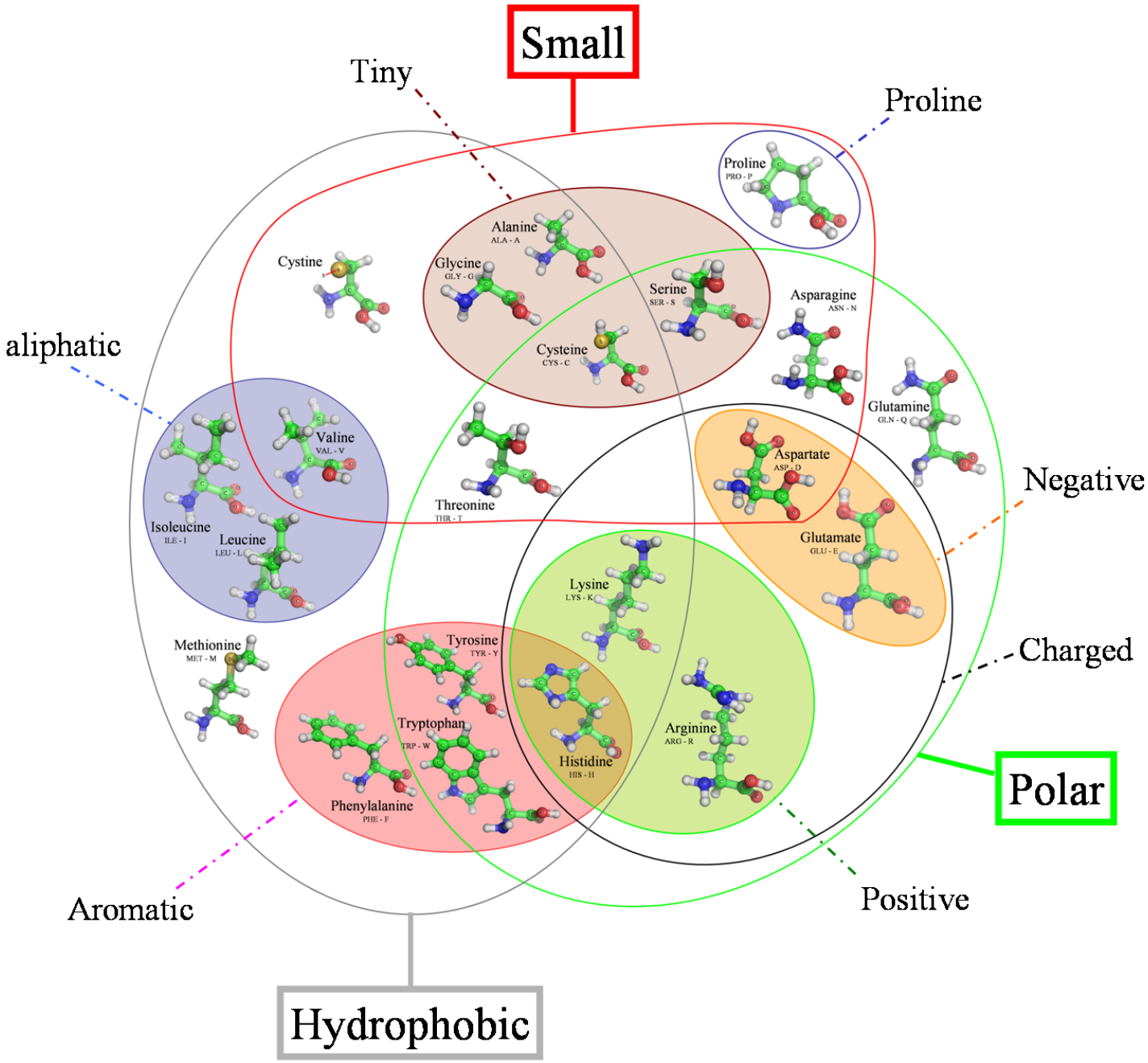
Acidic

Basic

Amino Acids

Name (Residue)	3-letter code	Single code	Relative abundance (%) E.C.	MW	pK	VdW volume(Å^3)	Charged, Polar, Hydrophobic
Alanine	ALA	A	13.0	71		67	H
Arginine	ARG	R	5.3	157	12.5	148	C+
Asparagine	ASN	N	9.9	114		96	P
Aspartate	ASP	D	9.9	114	3.9	91	C-
Cysteine	CYS	C	1.8	103		86	P
Glutamate	GLU	E	10.8	128	4.3	109	C-
Glutamine	GLN	Q	10.8	128		114	P
Glycine	GLY	G	7.8	57		48	-
Histidine	HIS	H	0.7	137	6.0	118	P,C+
Isoleucine	ILE	I	4.4	113		124	H
Leucine	LEU	L	7.8	113		124	H
Lysine	LYS	K	7.0	129	10.5	135	C+
Methionine	MET	M	3.8	131		124	H
Phenylalanine	PHE	F	3.3	147		135	H
Proline	PRO	P	4.6	97		90	H
Serine	SER	S	6.0	87		73	P
Threonine	THR	T	4.6	101		93	P
Tryptophan	TRP	W	1.0	186		163	P
Tyrosine	TYR	Y	2.2	163	10.1	141	P
Valine	VAL	V	6.0	99		105	H

Amino acid classes



Outline

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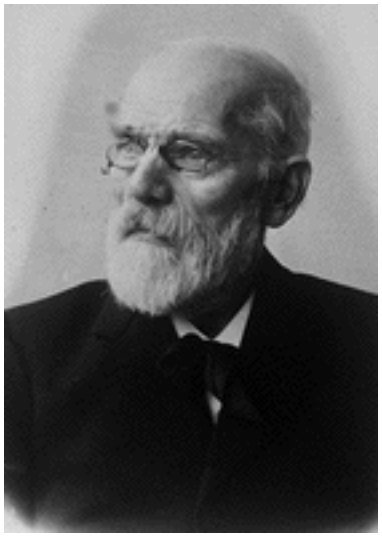
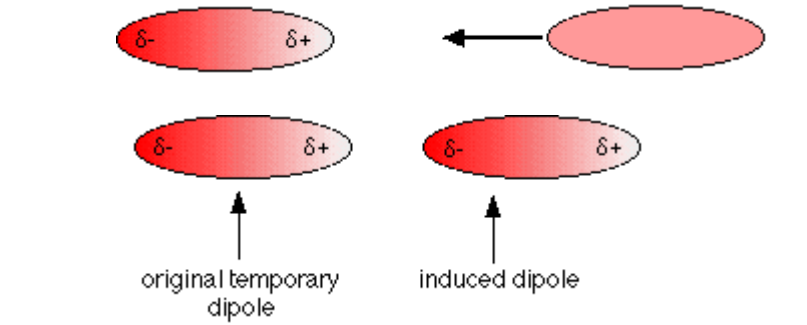
5. Physics of folding

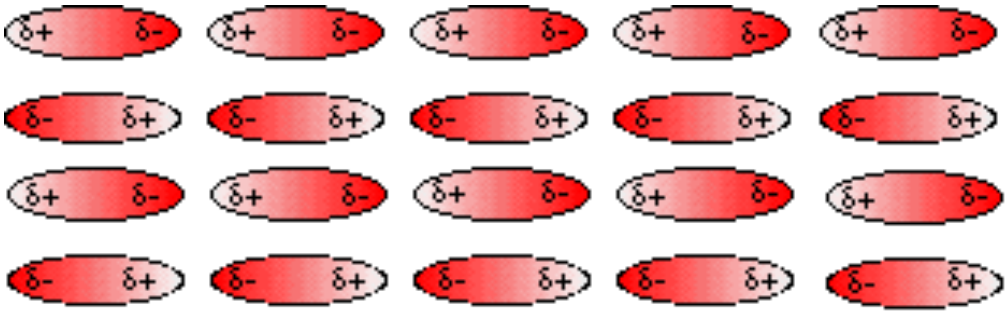
Forces

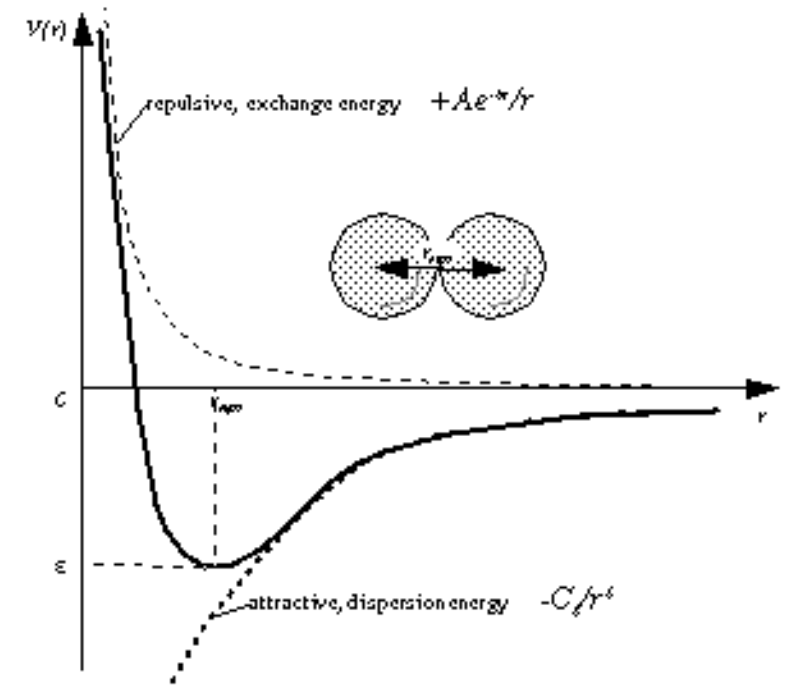
- Van der Waals
  "London forces" (after Fritz London)



Van der Waals





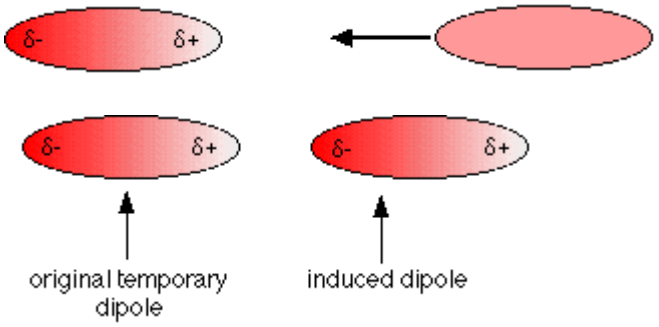


-0.2 kcal/mol at 4A

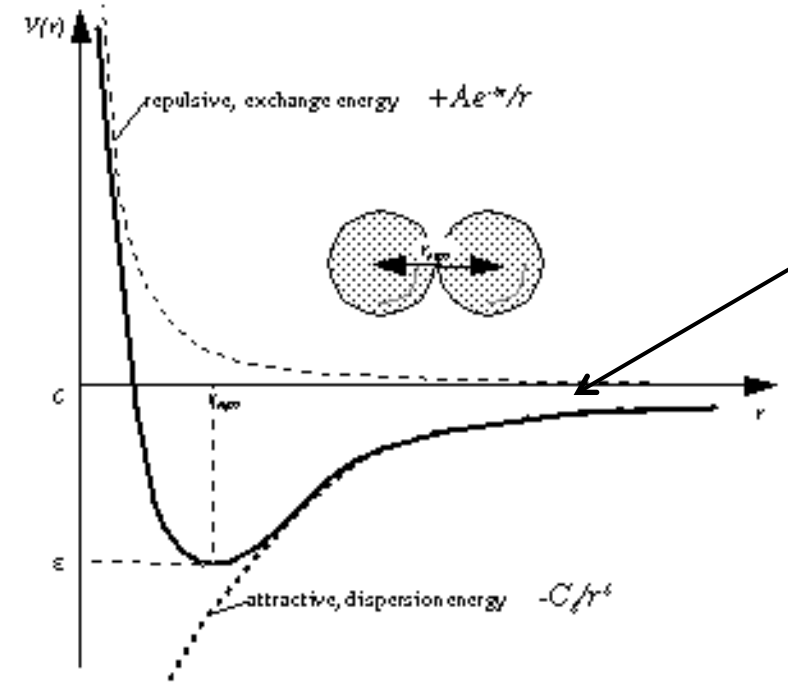
Casimir effect

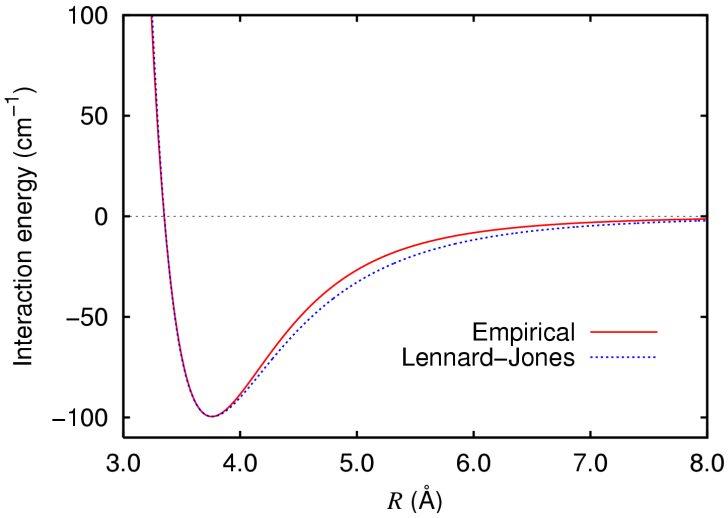
Forces

- Van der Waals : Lennard-Jones approximation



$$V(r) = \frac{A}{r^{12}} - \frac{B}{r^{6}}$$





Van der Waals interactions

Interaction	E_0 kcal/mol	r_0,A	r_{min},A	Atomic radii (A)	
H . . . . H	0.12	2.4	2.0	H:	1.0
H C	0.11	2.9	2.4		
C C	0.12	3.4	3.0	C:	1.5
O . . . . O	0.23	3.0	2.7	O:	1.35
N . . . . N	0.20	3.1	2.7	N:	1.35
CH_2 . . . CH_2	~ 0.5	~ 4.0	~ 3.0	CH_2:	~ 1.5

$$V(r) = \frac{A}{r^{12}} - \frac{B}{r^{6}} = E_0\left(\left(\frac{r_0}{r}\right)^{12} - \left(\frac{r_0}{r}\right)^{6}\right)$$

Van der Waals interactions

PNAS
Proceedings of the National Academy of Sciences of the United States of America www.pnas.org

Evidence for van der Waals adhesion in gecko setae

Kellar Autumn, Metin Sitti, Yiching A. Liang, Anne M. Peattie, Wendy R. Hansen, Simon Sponberg, Thomas W. Kenny, Ronald Fearing, Jacob N. Israelachvili, and Robert J. Full

PNAS published online Aug 27, 2002;
doi:10.1073/pnas.192252799

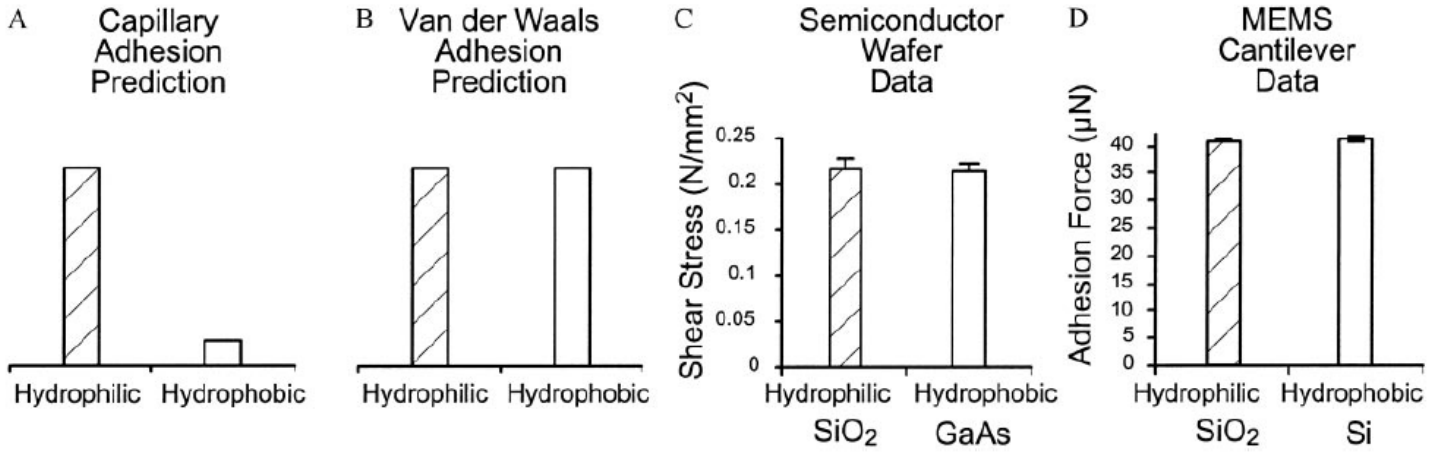
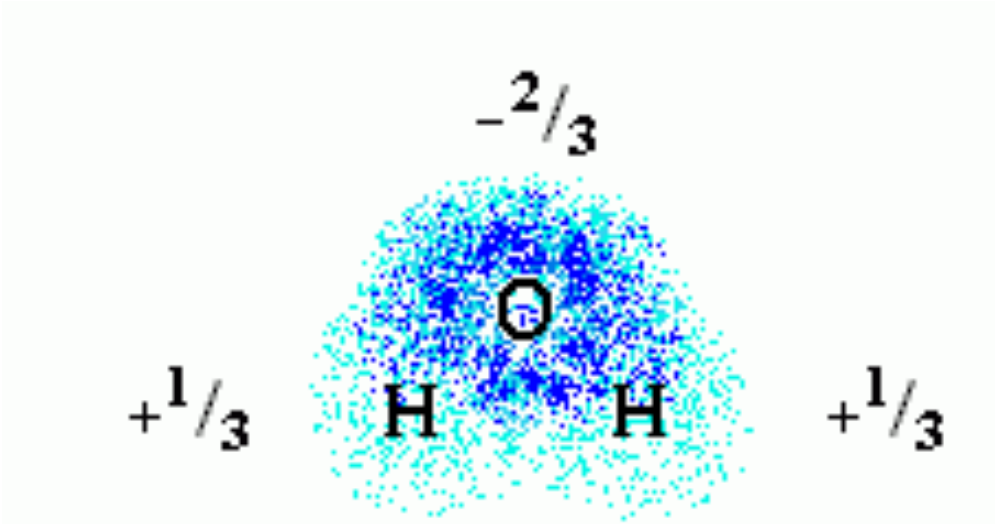


Fig. 1. Force of gecko setae on highly polarizable surfaces versus for surface hydrophobicity. (*A*) Wet adhesion prediction. (*B*) van der Waals prediction. (*C*) Results from toe on highly polarizable semiconductor wafer surfaces differing in hydrophobicity. (*D*) Results from single seta attaching to highly polarizable MEMS cantilevers differing in hydrophobicity. Note that geckos fail to adhere to hydrophobic, weakly polarizable surfaces [polytetrafluoroethylene where θ = 105° (25) and the dielectric constant, ε = 2.0 (23)]. Adhesion to hydrophilic and hydrophobic polarizable surfaces was similar. Therefore, we reject the hypothesis that wet, capillary interactions are necessary for gecko adhesion in favor of the van der Waals hypothesis.

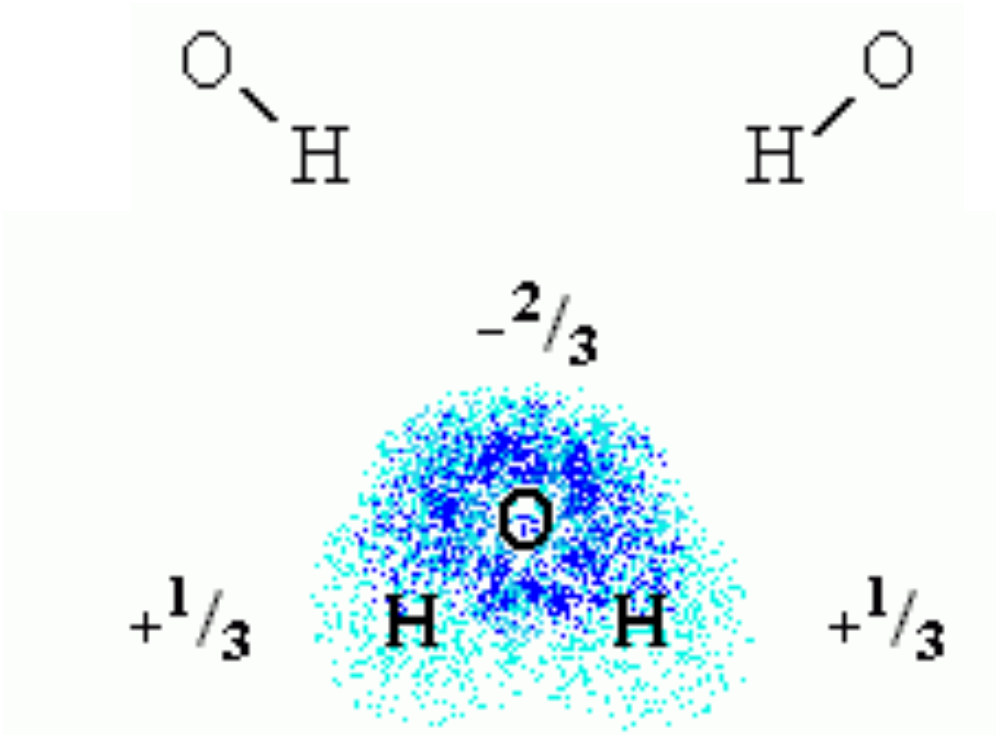
and 23) to predict R for the spatulae. We measured ≈40 μN adhesion per seta on MEMS surfaces. There are ≈3,600 tetrads of setae per mm^2 (39), or 14,400 setae per mm^2. Therefore, adhesive stress from our force measurements is ≈576,000 N/m^2 (5.68 atmospheres; 1 atm = 101.3 kPa). The Johnson–Kendall–

http://web.mit.edu/sangbae/www/media.html

Water and hydrogen bonds



Water and hydrogen bonds

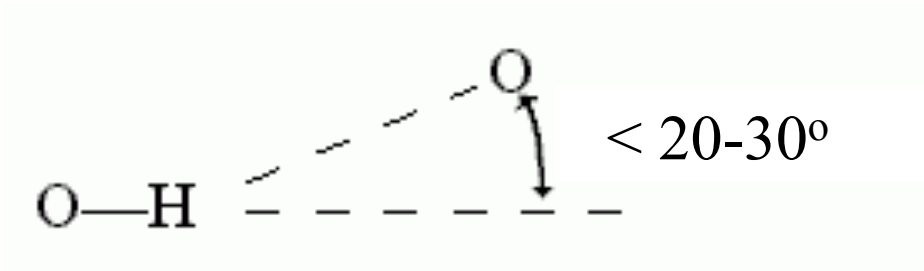


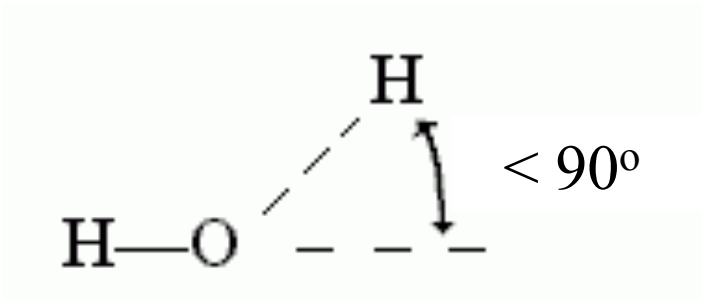
←1.8Å→
O—H : : : : : : O
← 2.8Å →

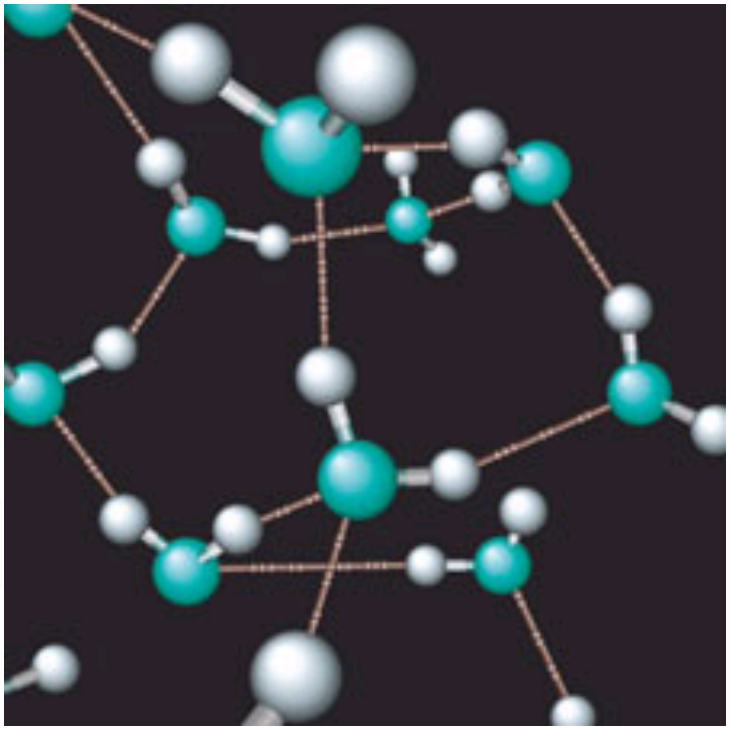
←1.9Å→
N—H : : : : : : O
← 2.9Å →

←2.1Å→
N—H : : : : : : N
← 3.1Å →

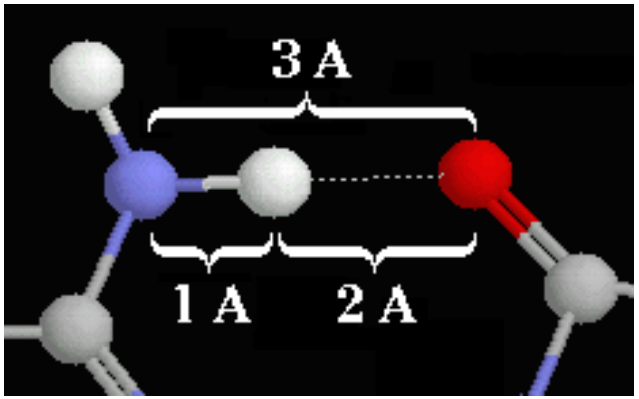
Hydrogen bonds : anisotropic







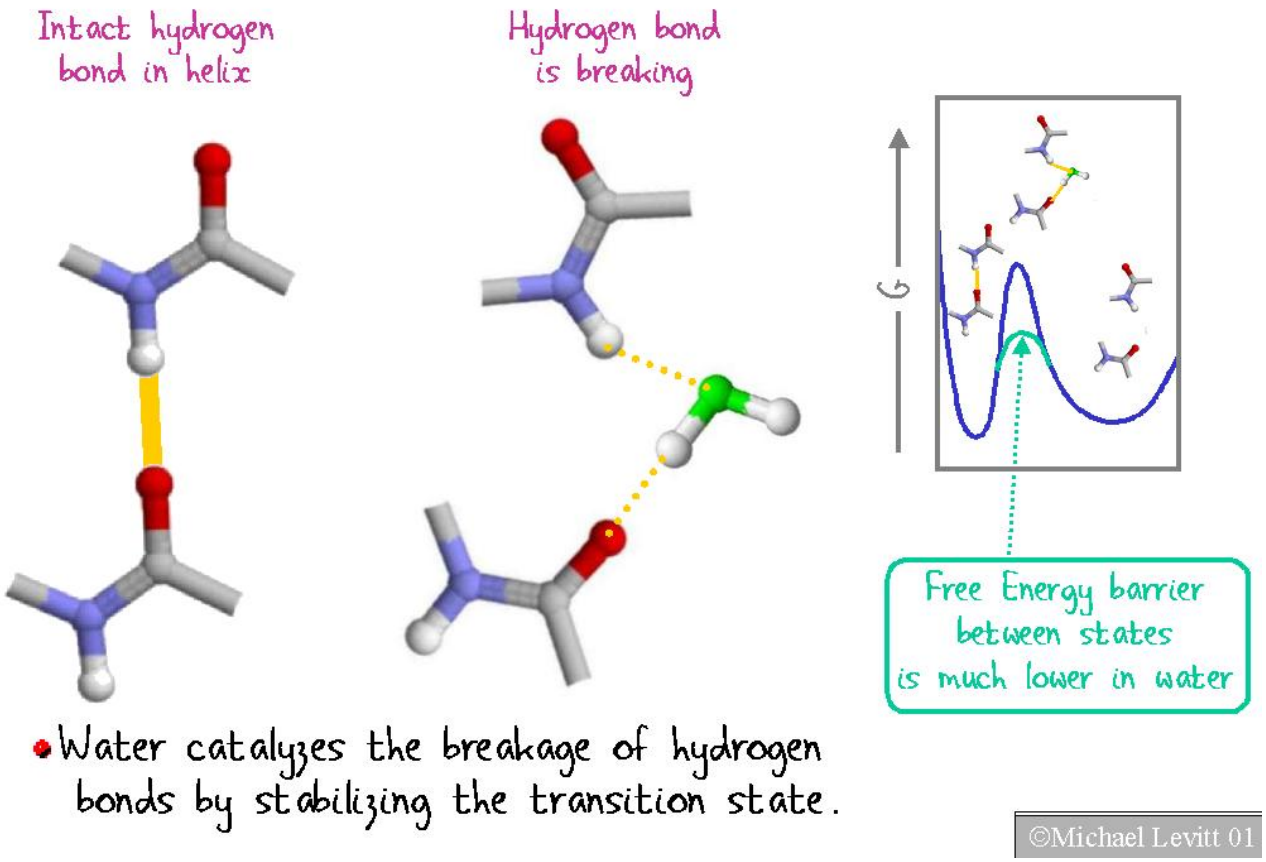
hydrogen bonds in water



Typical hydrogen bond within a protein.

SOLVENT: Hydrogen bonds

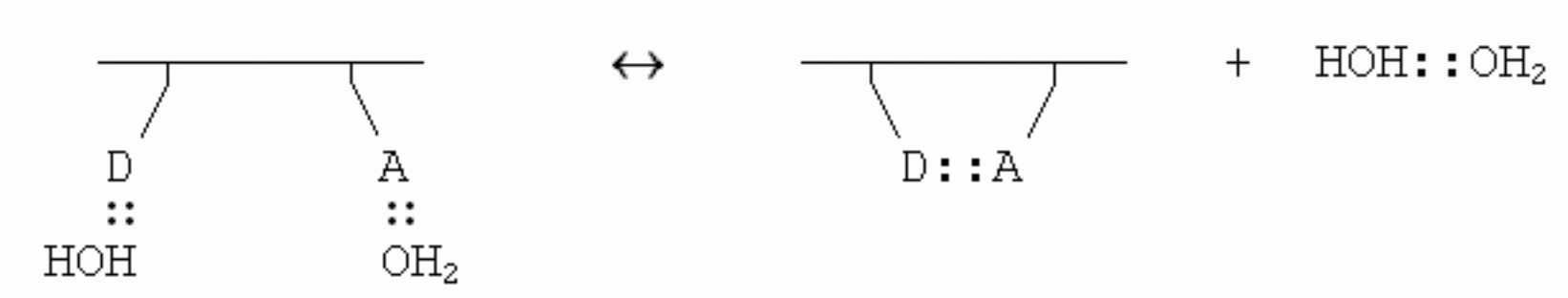
1. WATER ALLOWS HYDROGEN BONDS TO BREAK



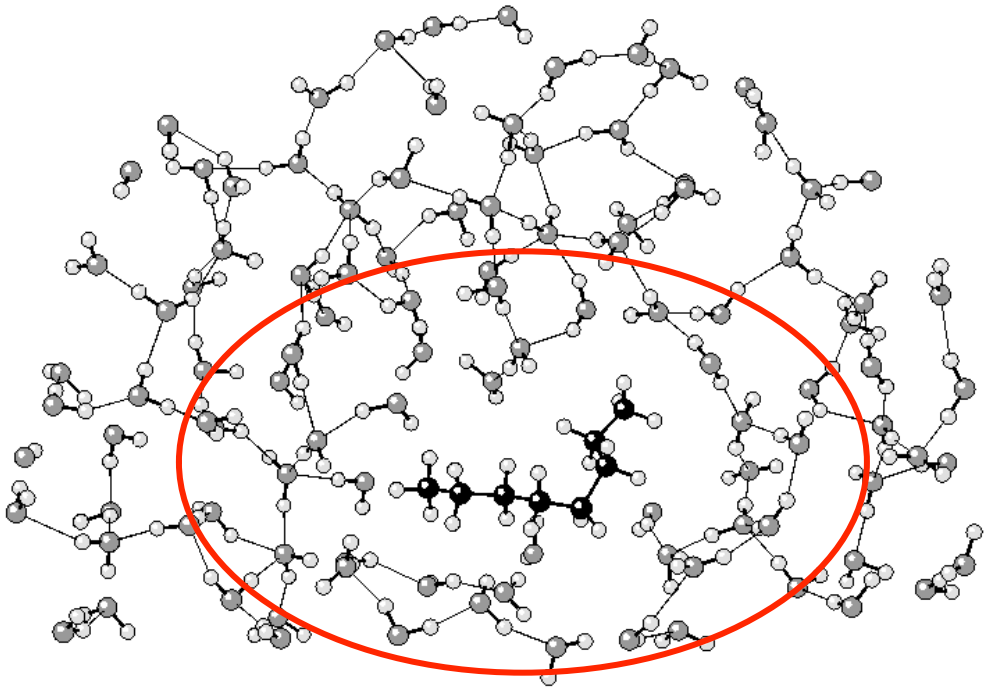
2. Hydrogen bonds in proteins are ENTROPIC

SOLVENT: Hydrogen bonds

2. Hydrogen bonds in proteins are ENTROPIC



Hydrophobic effect



Frank & Evans 1945

- Water molecules form hydrogen bonds
- Polar groups do not disturb the network of water-water interactions.
- Non-polar (hydrophobic) groups disrupt the network leading to formation of "local ordering" of water.
- Local ordering reduces the entropy

DG≈0.2 kcal/mol due to ordering of the interface water
compare to DG of breaking 1 H-bond = 5 kcal/mol

From: Laidig, K. E.; Daggett, V. *J. Phys. Chem.*, **1996**, *100*, 5616.

Hydrophobic effect

- (Walter Kauzmann 1959)
  Entropic (<1nm) and
  entalpic (>1nm)

Substitution	Number of examples	ΔΔG (kcal/mol)[c] Low	High	Average	ΔG_{tr}[d] (kcal/mol)
Ile → Val	9	0.5	1.8	1.3 ± 0.4	0.80
Ile → Ala	9	1.1	5.1	3.8 ± 0.7	2.04
Leu → Ala	17	1.7	6.2	3.5 ± 1.1	1.90
Val → Ala	11	0.0	4.7	2.5 ± 0.9	1.24
$-CH_2-$[b]	46	0.0	2.3	1.2 ± 0.4	0.68
Met → Ala	4	2.1	4.6	3.0 ± 0.9	1.26
Phe → Ala	4	3.5	4.4	3.8 ± 0.3	2.02

~10 cal/mol/A^2

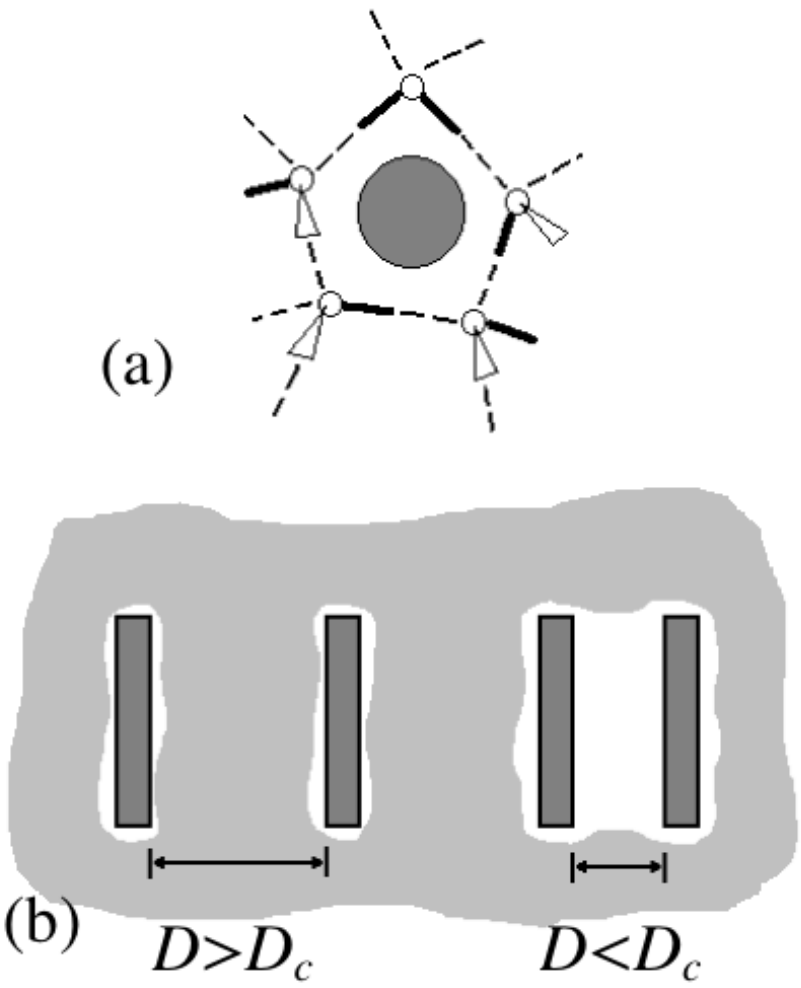


FIG. 1. a. Schematic view of local water structure near a small hydrophobic sphere. Dashed lines indicate hydrogen bonds. b. Schematic view of water structure near large parallel hydrophobic plates. Shaded area indicates regions where water density is essentially that of the bulk liquid; vacant regions indicate where water density is essentially that of the bulk vapor.

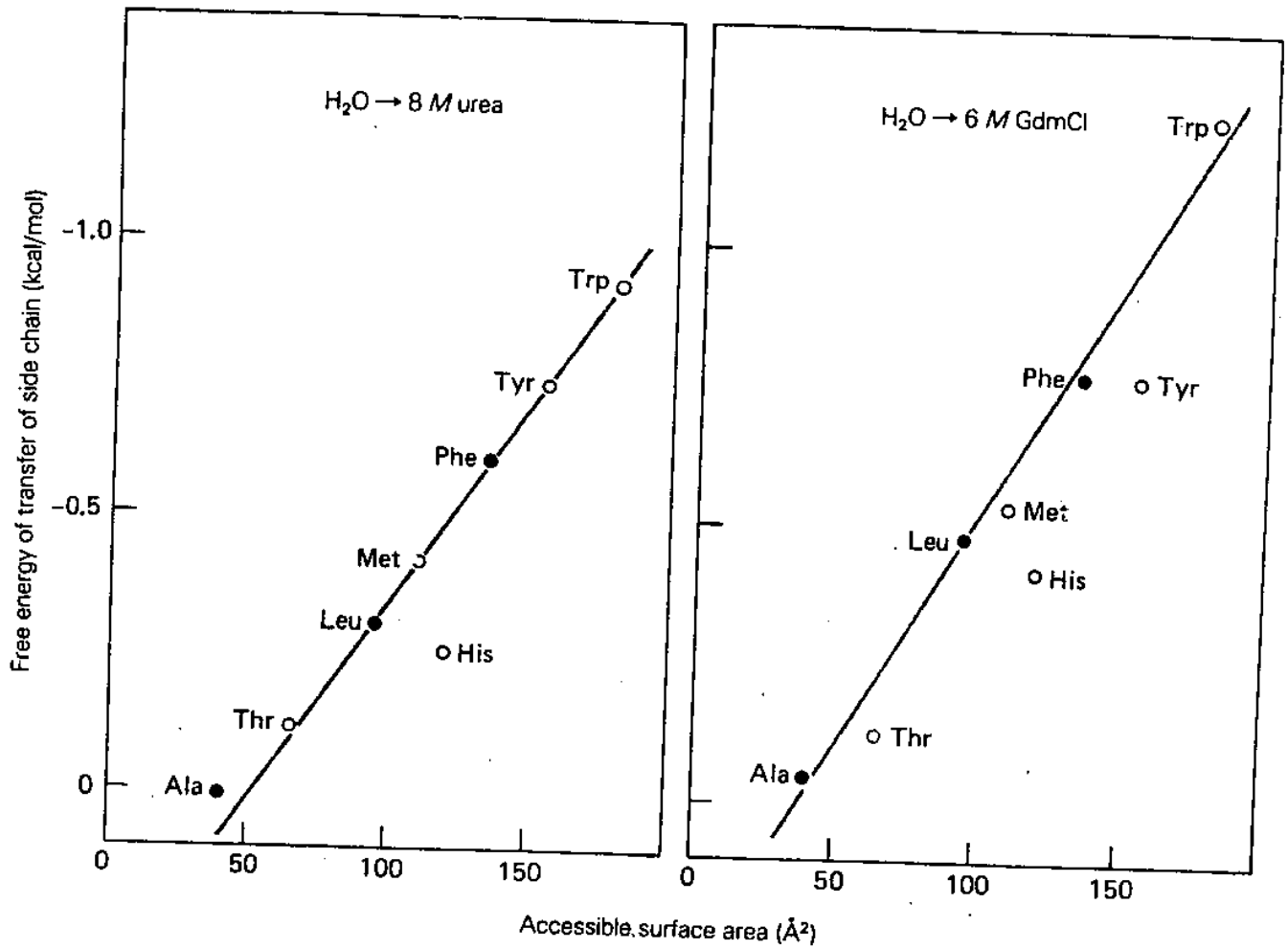
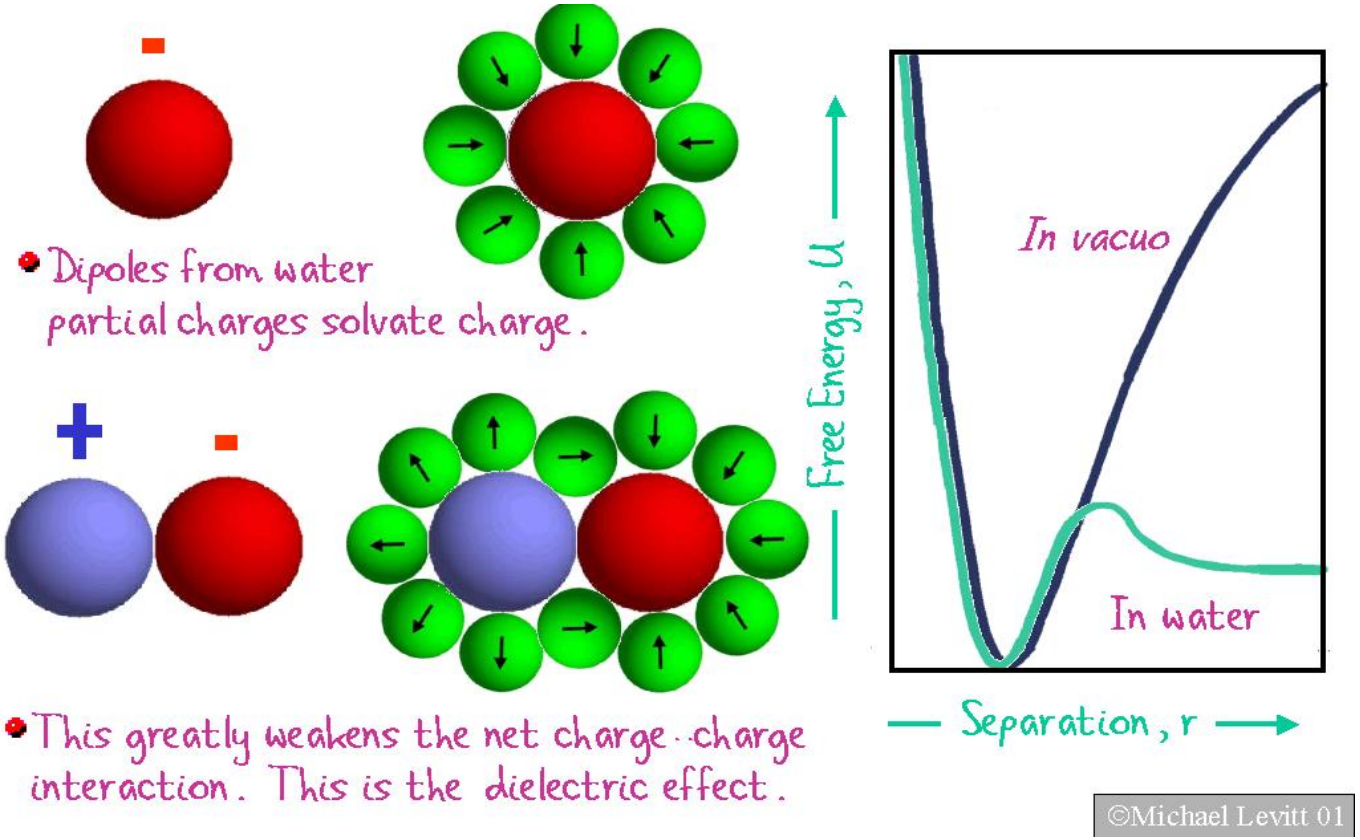


FIGURE 7.16

The denaturants urea and guanidinium chloride (GdmCl) increase the solubilities of both polar and nonpolar amino acid side chains, as measured by the free energy of transfer from water to either denaturant solution (Y. Nozaki and C. Tanford, *J. Biol. Chem.* 238:4074–4081, 1963; 245:1648–1652, 1970). There is a linear correlation of this effect with their accessible surface areas (Table 4.4), although the curves do not extrapolate through the origin. The solid lines have slopes of 7.1 and 8.3 cal/(mol · Å²) for 8 *M* urea and 6 *M* GdmCl, respectively. Residues indicated by open circles have polar groups on side chains. (From T. E. Creighton, *J. Mol. Biol.* 129:235–264, 1979.)

ELECTRO + SOLVENT : Dielectric effect

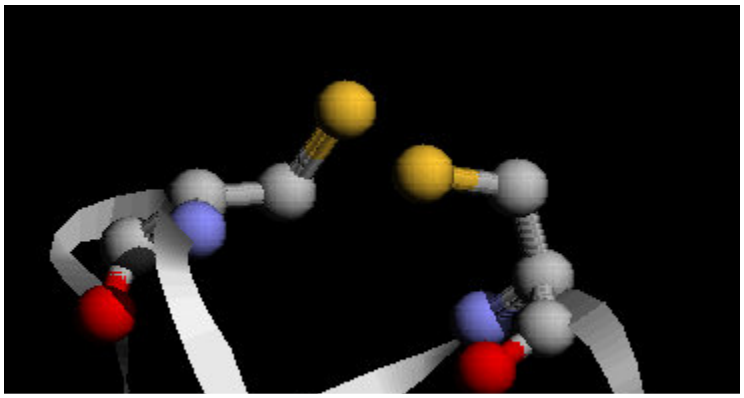
$$V = \frac{q_i q_j}{4\pi\,\varepsilon\, r_{ij}}; \qquad \varepsilon = 80$$



~2 Kcal/mol
$\Delta G \sim T$

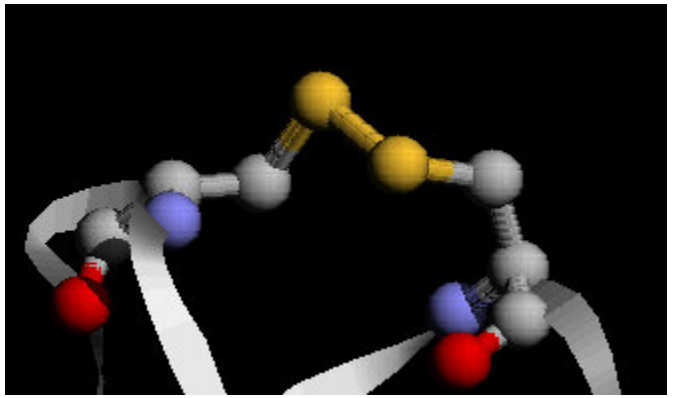
Linear in T
=> entropic!

In proteins only: Disulfide bonds (S-S bonds)



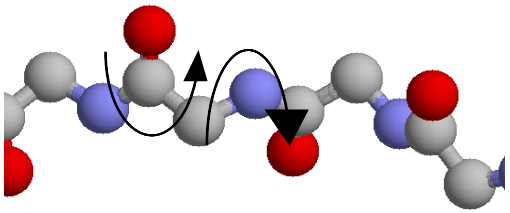
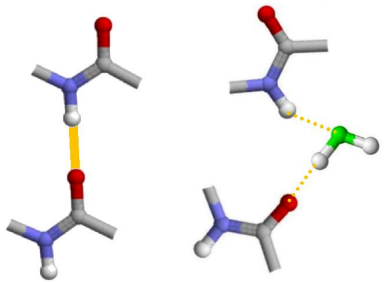
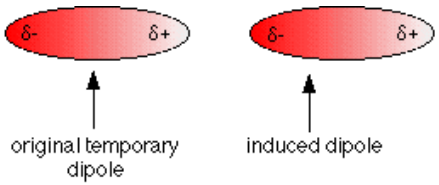
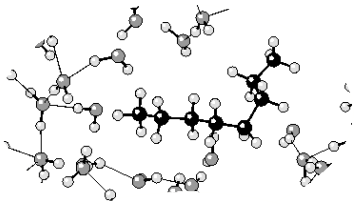
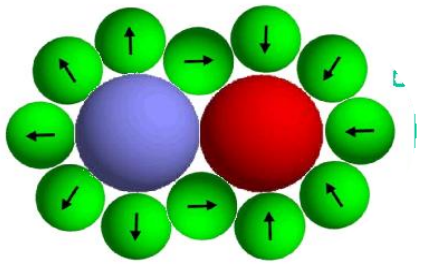
Oxidize

Reduce



CYS side chain : $-CH_2-SH$

SUMMARY: Biomolecular forces

Rotation f,	*quantum*		1 Kcal/mol
H-bonds	*entropic*		0.5 Kcal/mol
VdWaals	*quantum*		0.2 Kcal/mol
Hydrophobic	*entropic*		1.5 Kcal/mol ~10 cal/mol/A^2
Electrostatic	*entropic!*		2-3 Kcal/mol

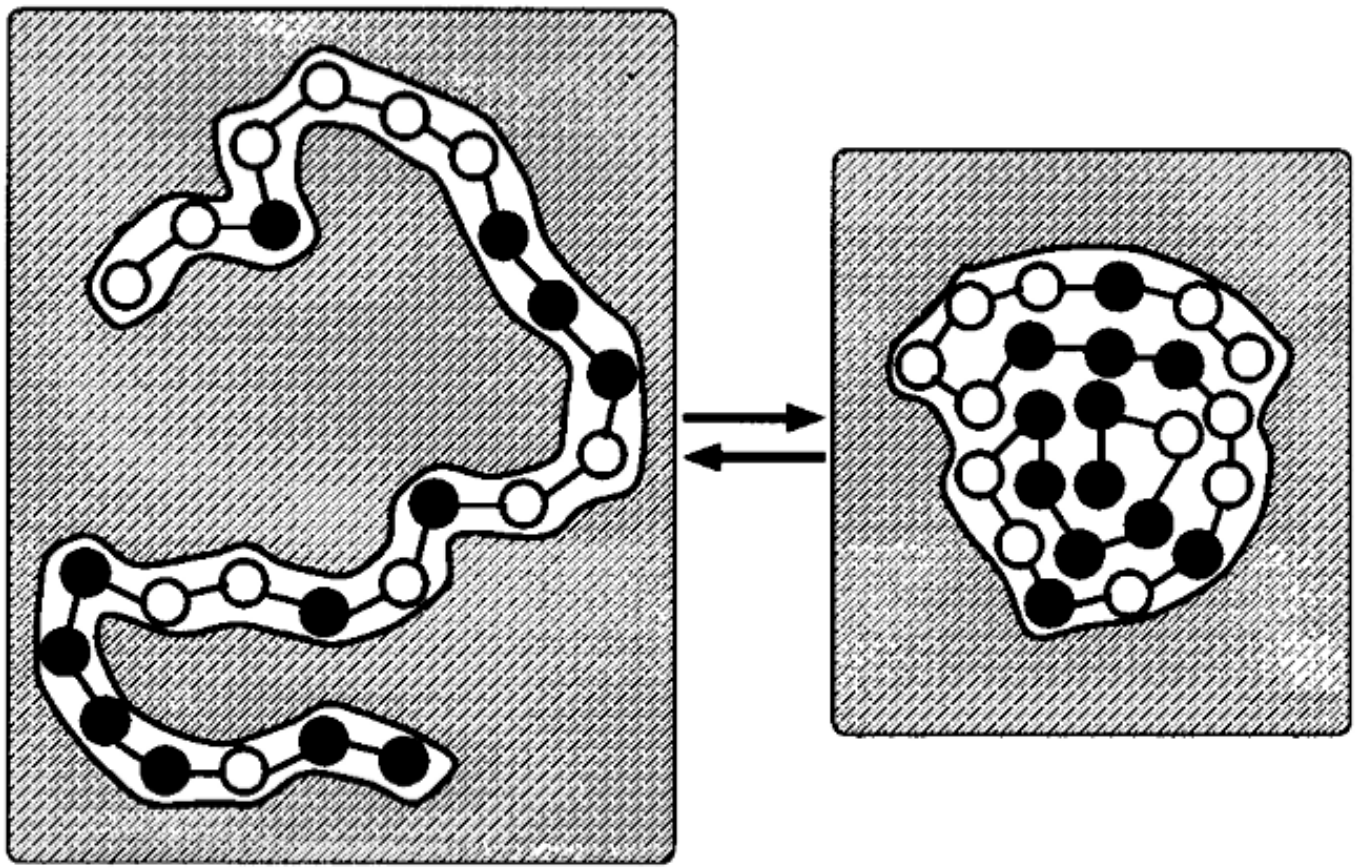


Fig. 3. Schematic of protein-folding equilibrium. The black and white circles represent hydrophobic and hydrophilic residues, respectively. The shaded region depicts aqueous solution.

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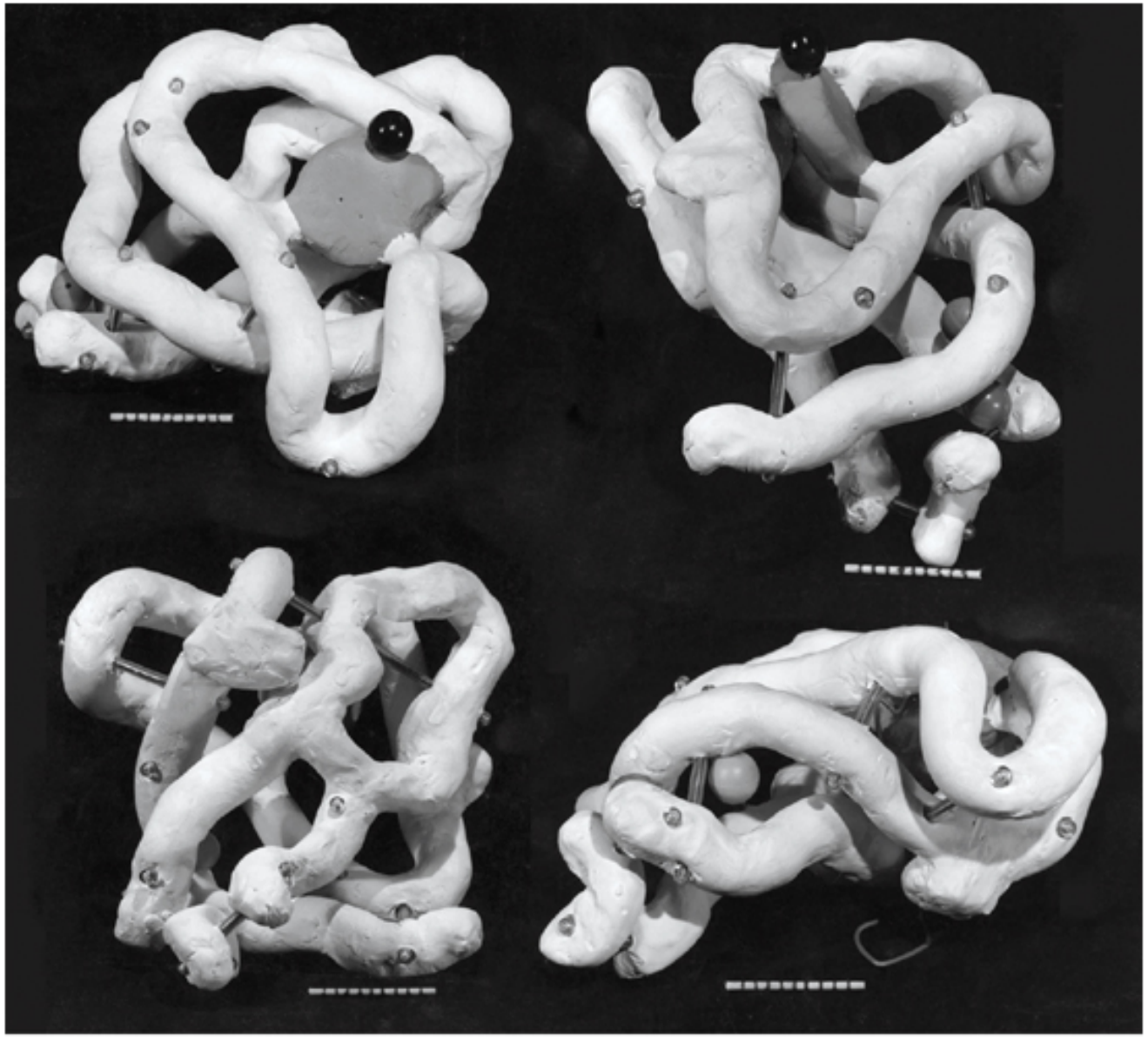

Nature Reviews | Molecular Cell Biology

The low-resolution structure of myoglobin that was published by John Kendrew and colleagues in 1958

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Molecule of the Month:
Riboswitches

Why use two or more molecules when one will do? In our own cells, protein synthesis is controlled by thousands of regulatory proteins, which work together to decide when a particular protein will be made. Bacteria are masters of economy, however, and in some cases, they have figured out a way for messenger RNA to control itself, without the need for help by proteins.

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BindingDB data are available from Structure Summary pages and through Advanced Search.

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- **Analyze small molecule interactions in the PDB with Ligand Explorer**

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Secondary Structure: b-sheets

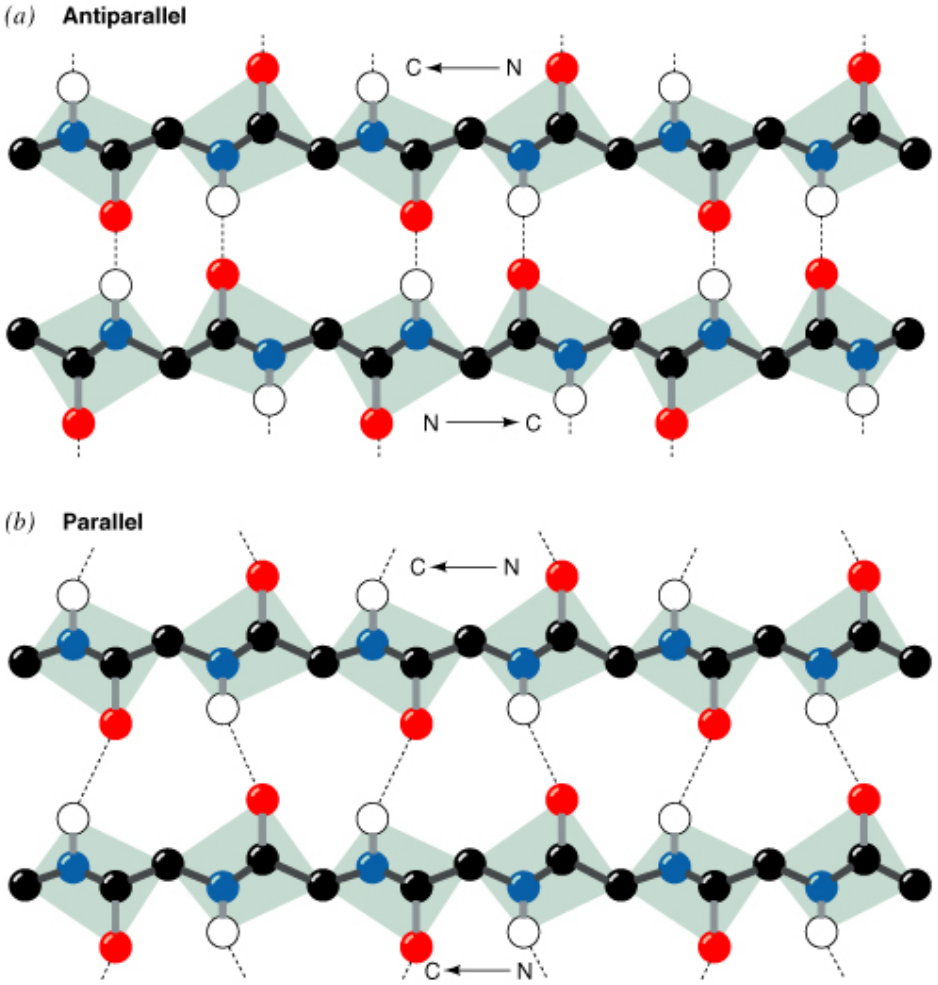
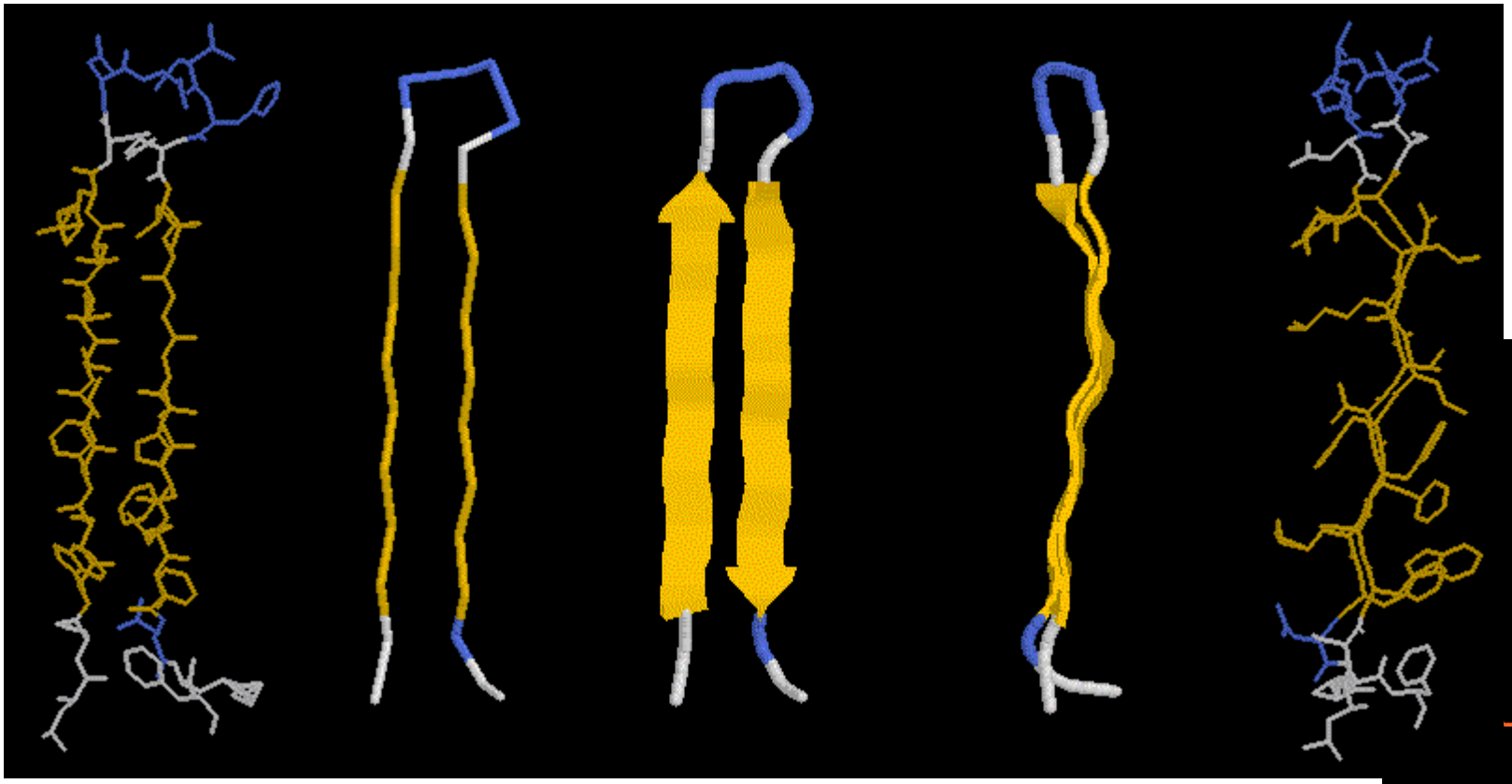
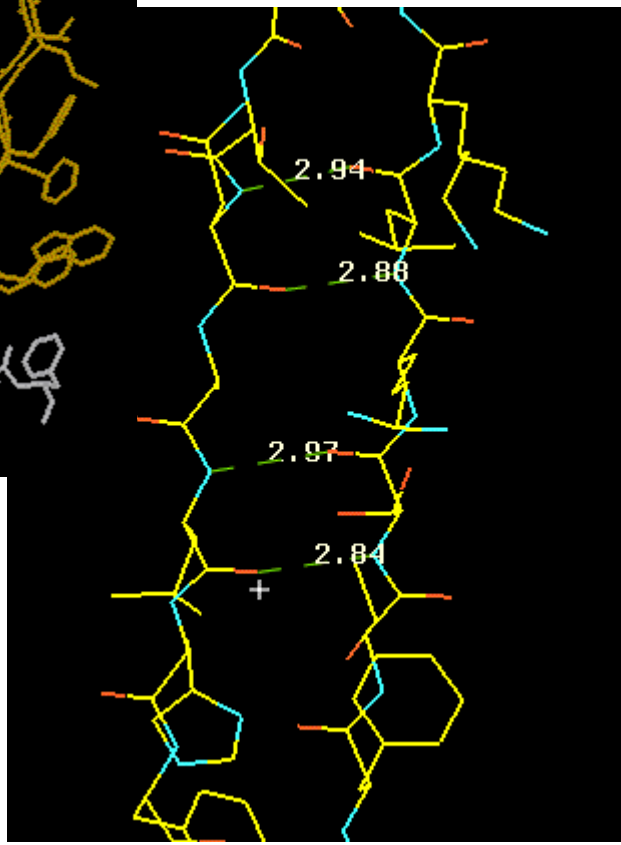


Figure 6-9. Key to Structure. ß Sheets.
[Figure copyrighted © by Irving Geis.]

Secondary Structure:
b-sheets





Secondary Structure: a-helices

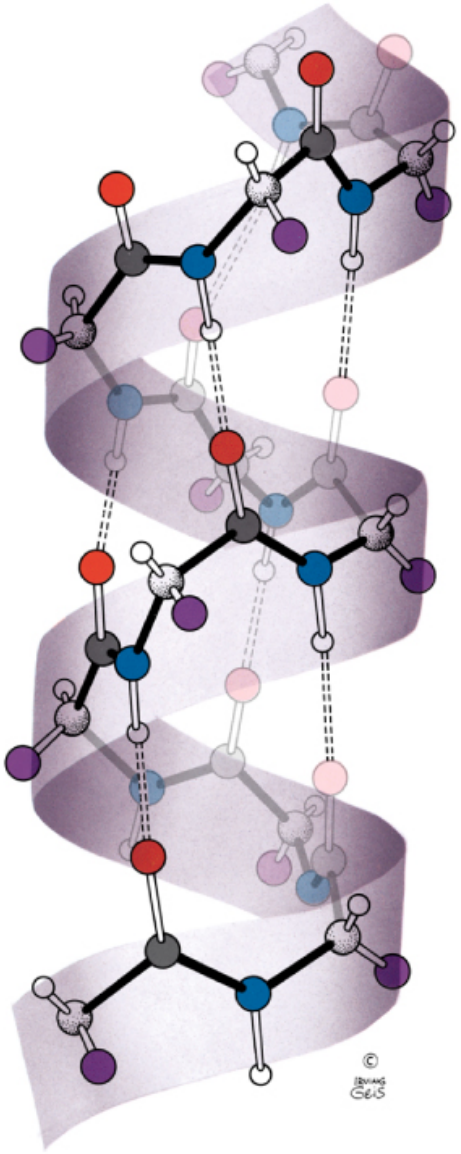
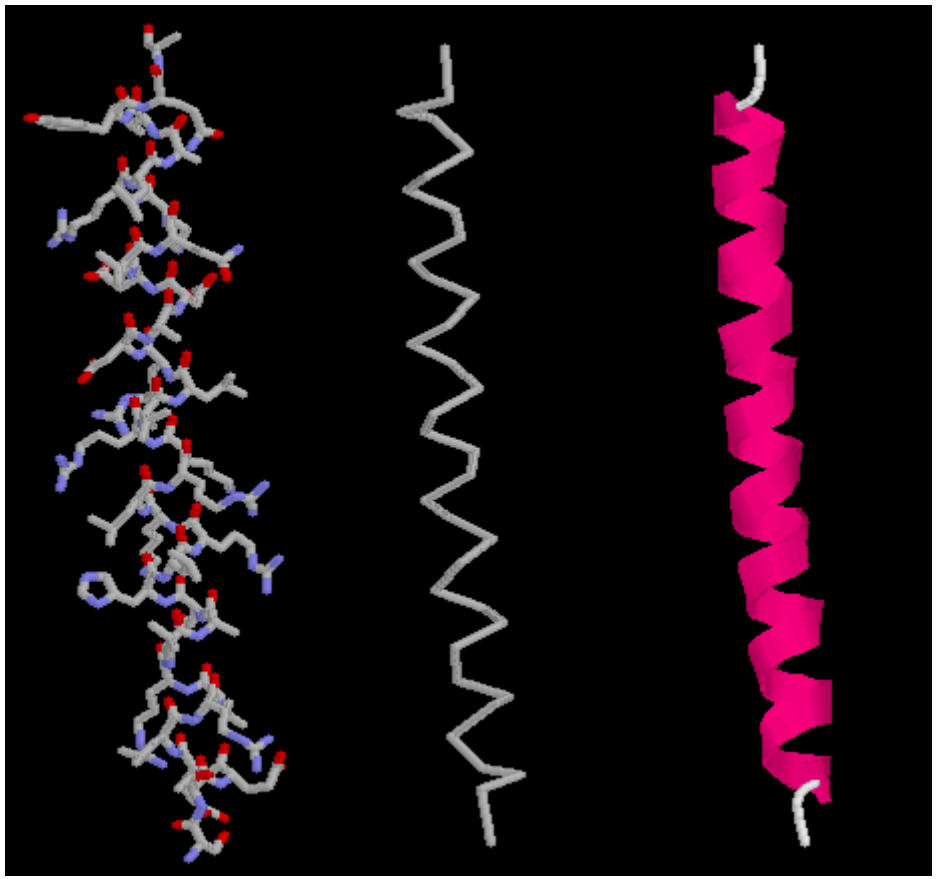
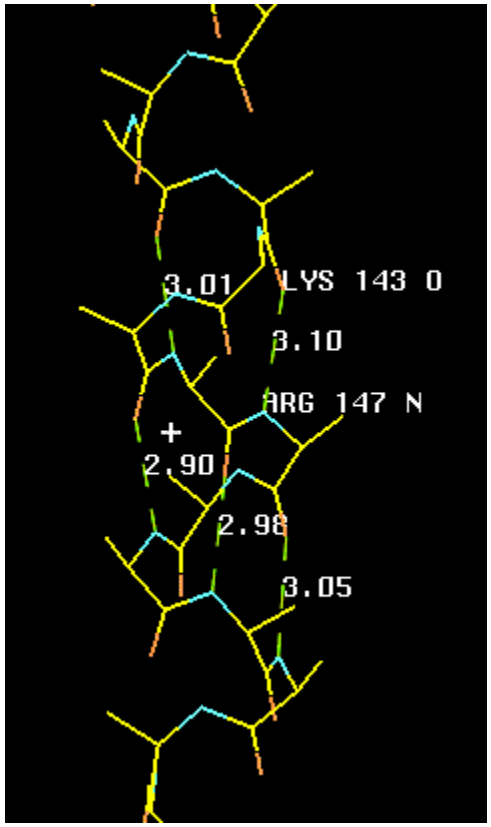
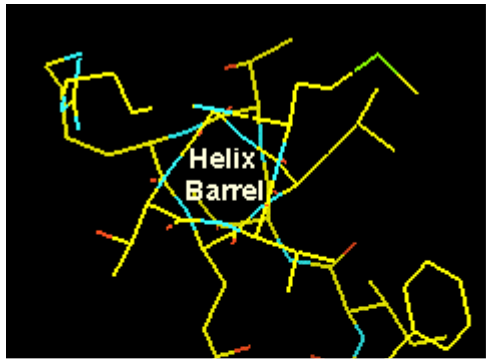


Figure 6-7. Key to Structure. The α helix.
[Figure copyrighted by © Irving Geis.]

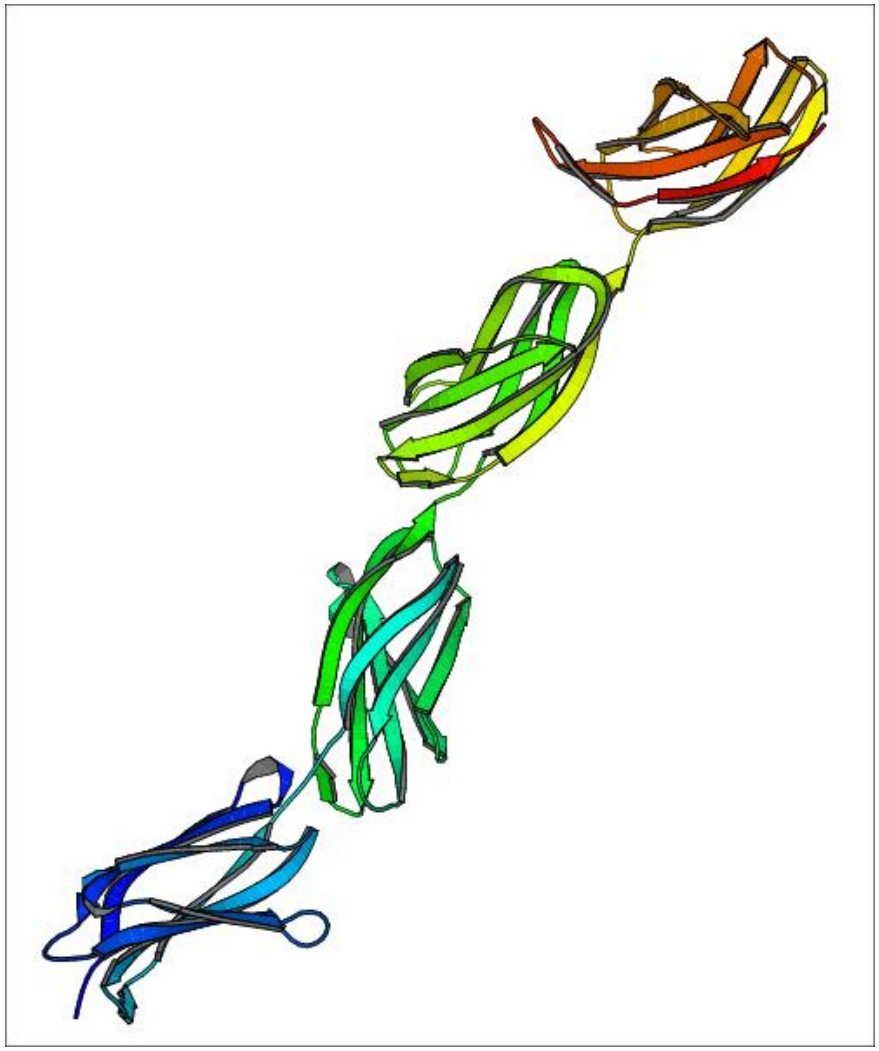
Secondary Structure: a-helices



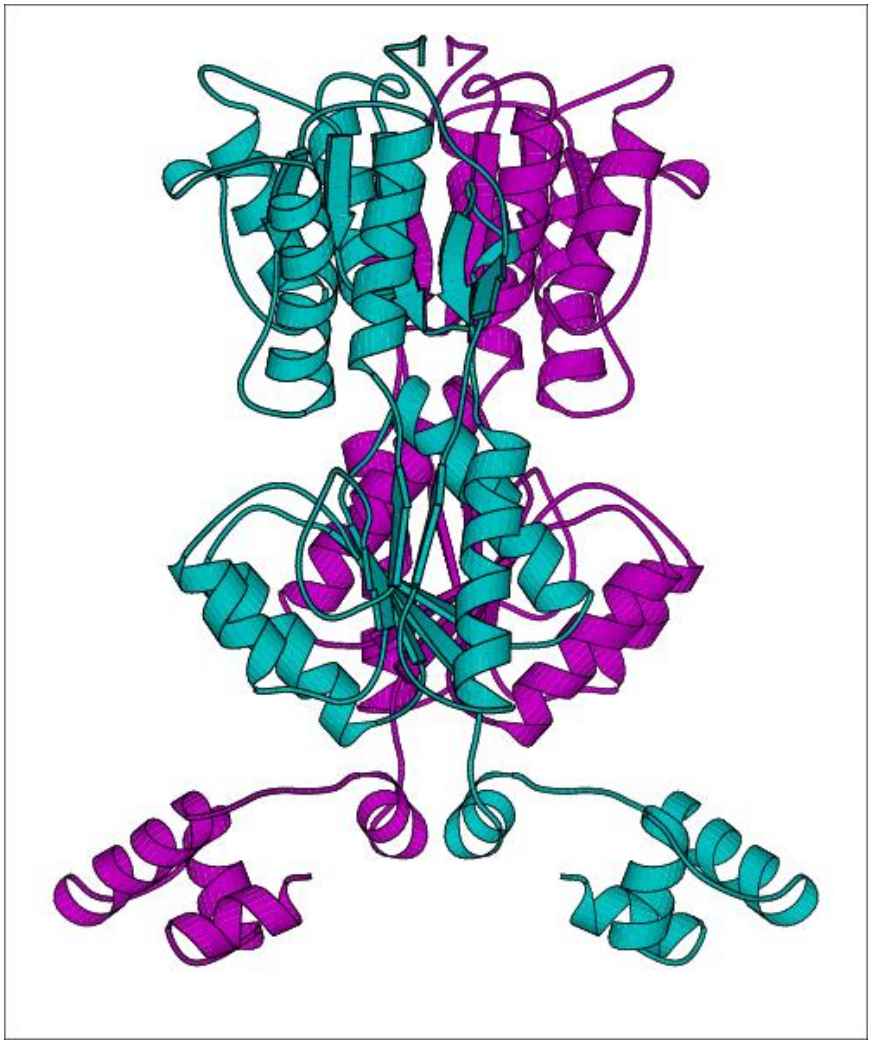




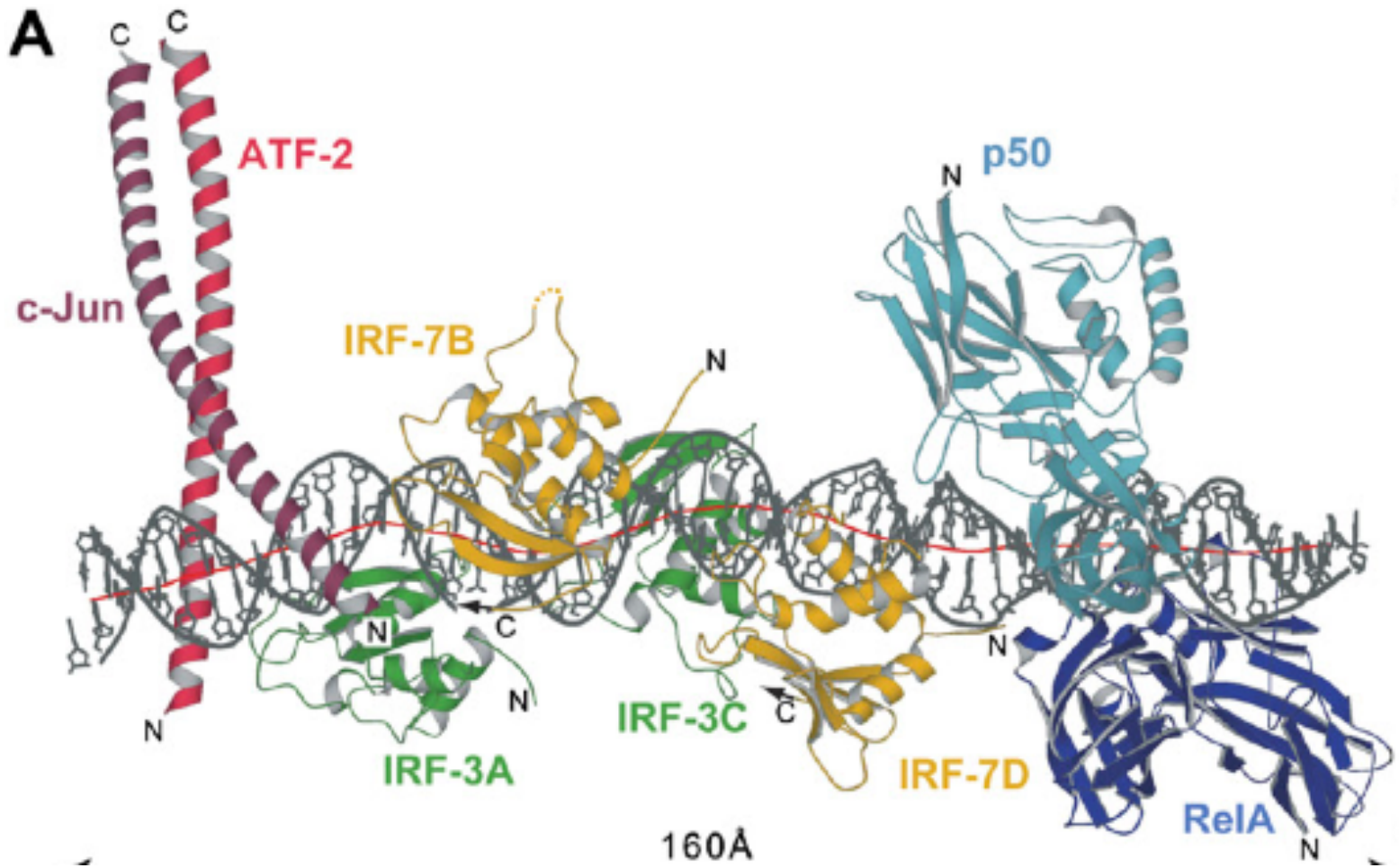
Domain Structure



MANY PROTEINS CONSIST OF SEVERAL DOMAINS



MANY PROTEINS ARE DIMERS OR OLIGOMERS WHICH CONSIST OF SEVERAL POLYPEPTIDE CHAINS.



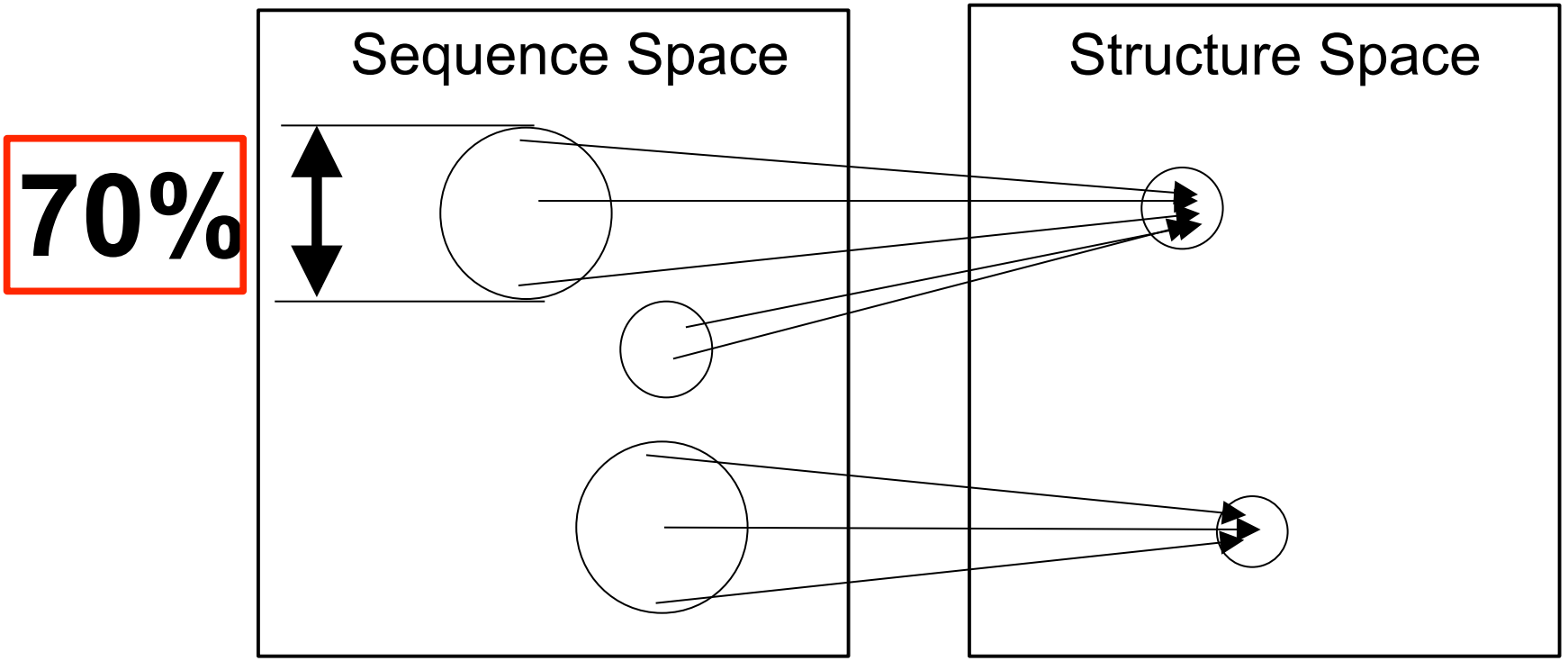
An Atomic Model of the Interferon-β Enhanceosome

Daniel Panne,[1] Tom Maniatis,[2] and Stephen C. Harrison[1,*]

Cell

Sequence–Structure Mapping

- Similar sequences always have similar structures.
- Different sequences have different structures, **but**
- Different sequences may have similar structures.



Protein Folding Problem

- **HOW DOES A PROTEIN FOLD?**

  Levinthal Paradox:

  A protein of 100 amino acids has ~ 4^{100} ~ 10^{62} possible conformations. Folding by trying each conformation in 10^{-12} sec will take 10^{44} years!

  BUT it takes a protein only 10^{-1}..10^{-2} seconds to fold...

- **PREDICT PROTEIN STRUCTURE FROM IT SEQUENCE.**

  Is information contained in protein sequence sufficient to determine protein structure?

  Anfinsen Experiment

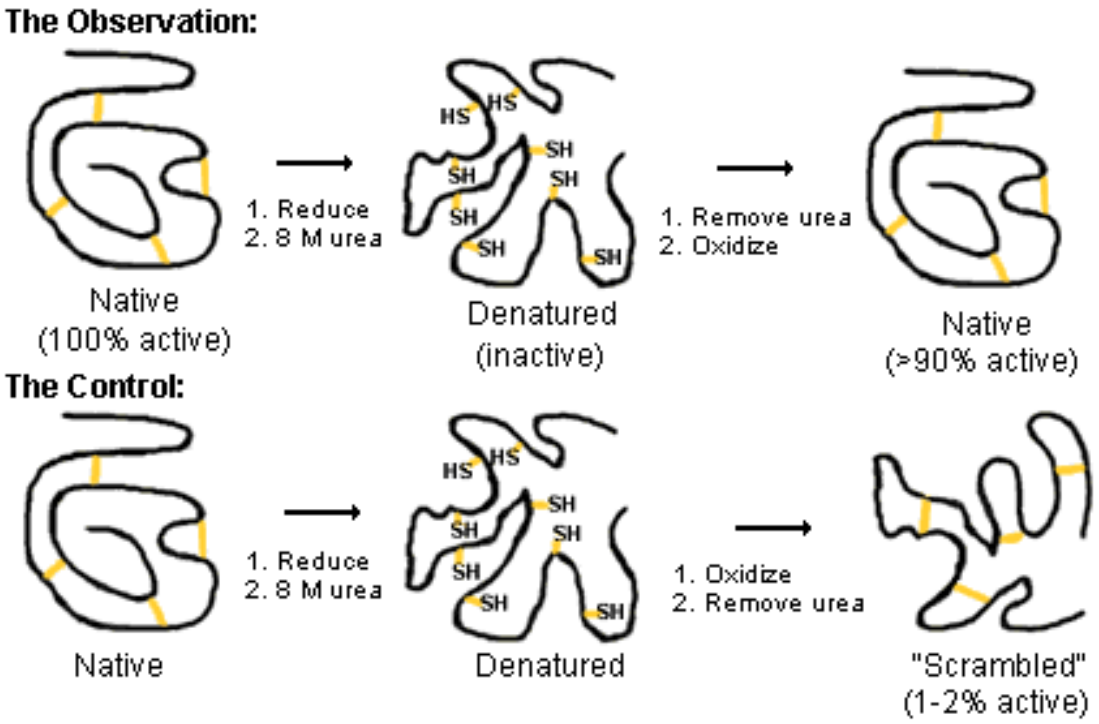
Protein Folding

Levinthal Paradox

A protein of 100 amino acids has ~ 4^{100} ~ 10^{62} possible conformations. If it takes 10^{-12} sec to try each conformation, then it takes 10^{44} years to find the native one!

BUT proteins fold in $10^{-1}..10^{-2}$ sec.

Anfinsen Experiment



- Information contained in the protein sequence is sufficient to determine protein structure!
- THERMODYNAMIC HYPOTHESIS:
  The native structure is the GLOBAL minimum of free energy.

Anfinsen, C.B. (1973) "Principles that govern the folding of protein chains." *Science* **181** 223-230.