

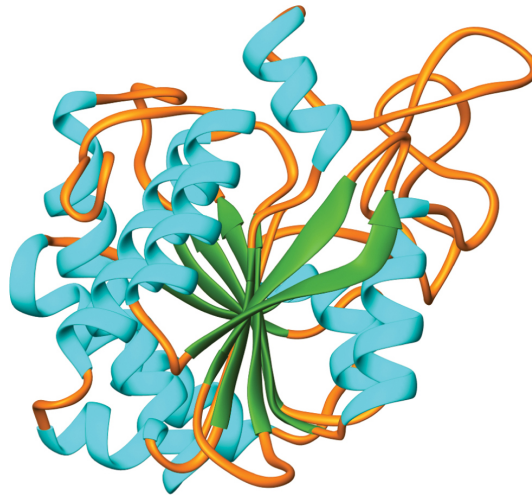
I. Protein Structure A. Primary 1. Peptide Bond 2. Determination B. Secondary 1. α-Helix 2. β-sheets/strands 3. Connections between β-strands 4. Super secondary structure C. Tertiary 1. Picturing and classifications 2. Topology 3. Domains 4. Intrinsically disordered 5. Stability D. Quaternary II. Protein-Conformational Structure Determination A. Quaternary structure 1. How determined; Gel filtration & SDS-PAGE, Ultracentrifugation B. Tertiary structure 1. X-ray diffraction/crystallography 2. NMR spectroscopy 3. Comparison: NMR <i>versus</i> X-ray crystallography C. Secondary structure 1. Circular dichroism (CD)	Lecture 10 (10/1/25) • Reading: Ch4; 116-117, 126-128 • Homework #10 NEXT • Reading: Ch4; 116, 138-142 • Homework #11
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Tertiary Structure

Bovine Carboxypeptidase A

Super-secondary motifs:

- $\beta\alpha\beta$
- Rossmann Fold
- β -hairpin
- $\alpha\alpha$
- Greek key
- β -meander
- β -barrel
- $\alpha\beta$ -barrel

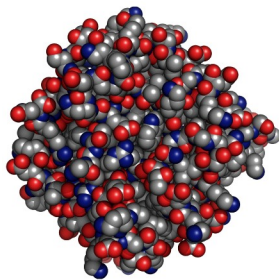


Based on an X-ray structure by William Lipscomb, Harvard University.
PDBid 3CPA.

Carboxypeptidase A
PDBid [3CPA](#)

Protein Structure-Tertiary

Picturing protein structure



(a)

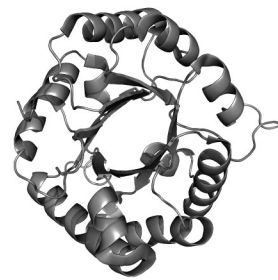
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Space-fill



(b)

Backbone trace



(c)

Ribbon

Triose-phosphate Isomerase (TIM)

4

Protein Structure-Tertiary

Picturing protein structure

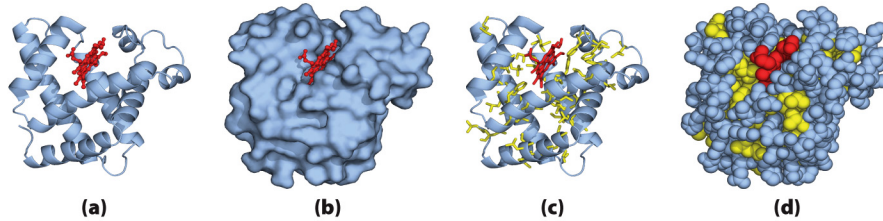


Figure 4-16
Lehninger Principles of Biochemistry, Seventh Edition
© 2017 W. H. Freeman and Company

Ribbon

Surface
contour

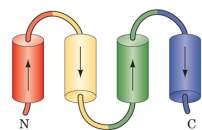
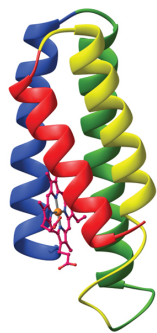
Ribbon with
side-chains

Space-
filling

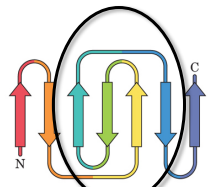
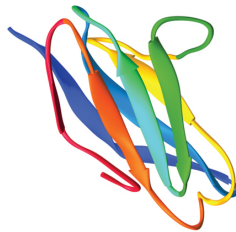
Sperm-whale Myoglobin (Mb)

Protein Structure-Tertiary

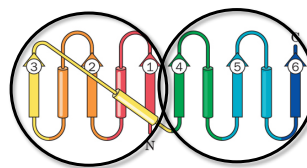
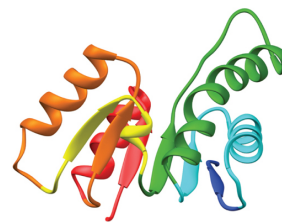
Protein Classification: α , β , α/β , or barrels



Cytochrome *b562*
PDBid [2S6B](#)



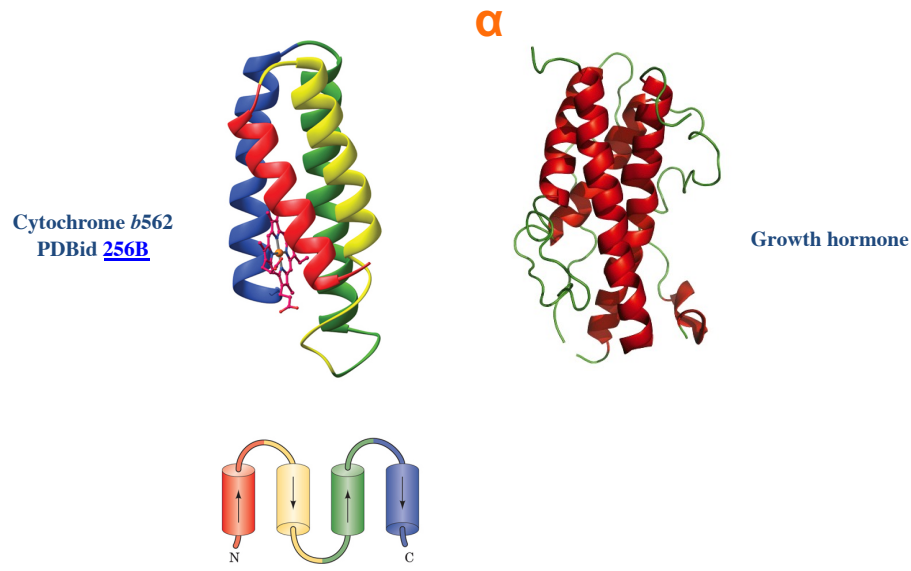
Human immunoglobulin fragment
PDBid [7EAB](#)



Dogfish lactate dehydrogenase domain 2
PDBid [6LDH](#)

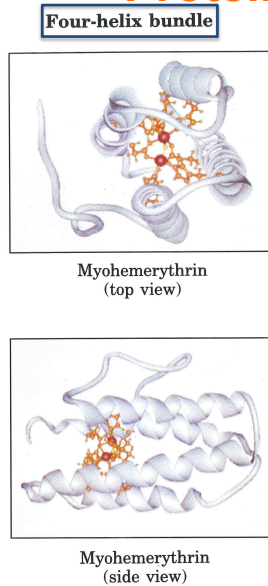
Protein Structure-Tertiary

Protein Classification:



Protein Structure-Tertiary

Protein Classification:

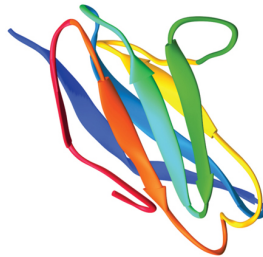


Protein Structure-Tertiary

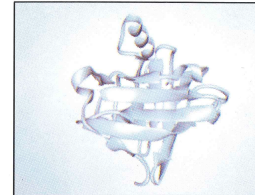
Protein Classification:

β

β - β Sandwich

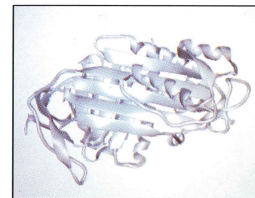
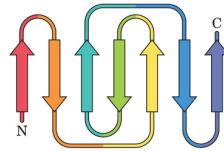


Human immunoglobulin fragment
PDBid [7FAB](#)



Insecticyanin

Immunoglobulin-fold



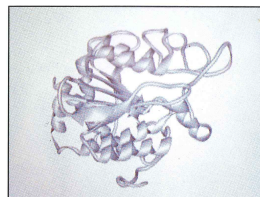
α_1 -Antitrypsin

Protein Structure-Tertiary

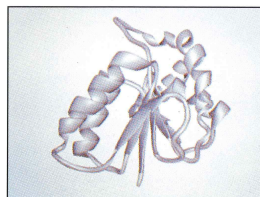
Protein Classification:

α/β

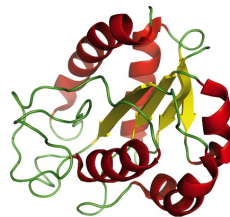
$\alpha\beta$ with saddle at core



Carboxypeptidase

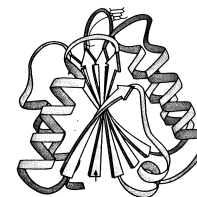


Lactate
dehydrogenase
domain 1

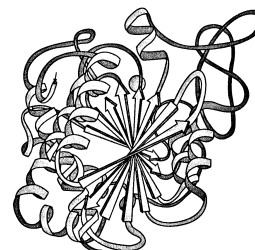


Flavodoxin

SADDLE SHAPE



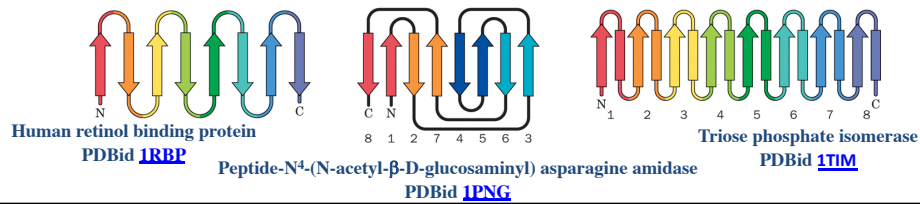
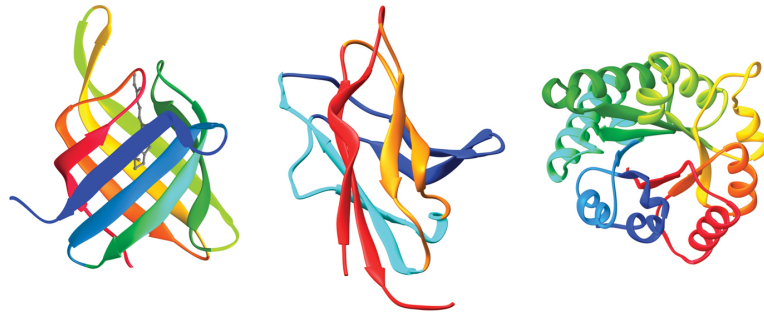
Flavodoxin



Carboxypeptidase
(b)

Protein Structure-Tertiary

Protein Classification: 8-Stranded Barrels (either β or α/β)



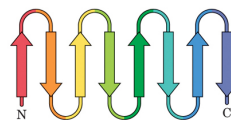
Protein Structure-Tertiary

Protein Classification: 8-Stranded Barrels (either β or α/β)

Human retinol binding protein
PDBid [1RBP](#)



β -meander



Protein Structure-Tertiary

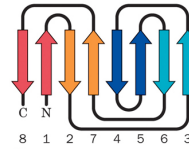
Protein Classification: 8-Stranded Barrels (either β or α/β)

Peptide-N⁴-(N-acetyl- β -D-glucosaminyI) asparagine amidase
PDBid [1PNG](#)



Greek key

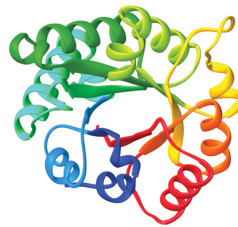
(4-5-6-7)
(1-2-7-8)



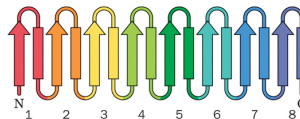
Protein Structure-Tertiary

Protein Classification: 8-Stranded Barrels (either β or α/β)

Triose phosphate isomerase
PDBid [1TIM](#)



α/β -barrel

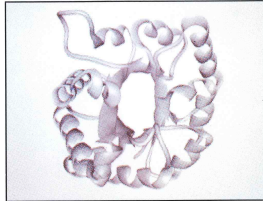


(Rossmann Folds (β - α - β - α - β))

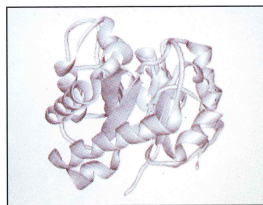
Protein Structure-Tertiary

Protein Classification: 8-Stranded Barrels (either β or α/β)

α/β Barrel



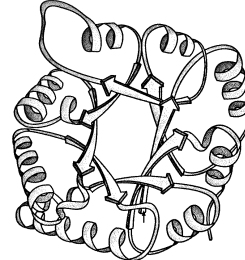
Triose phosphate isomerase
(top view)



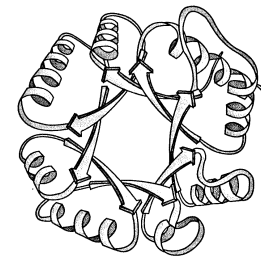
Triose phosphate isomerase
(side view)

α/β -barrels

β -BARREL SHAPE



Triose phosphate isomerase



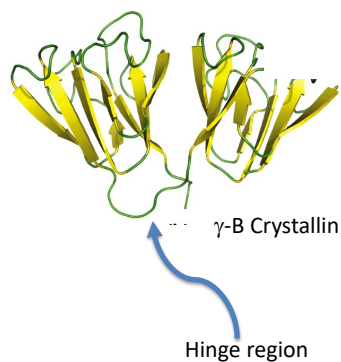
Pyruvate kinase domain 1
(a)

Protein Structure-Tertiary

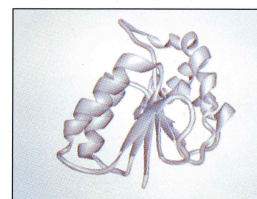
Protein Domains

Domains:

Separate folded structures with hinge
all with one polypeptide chain



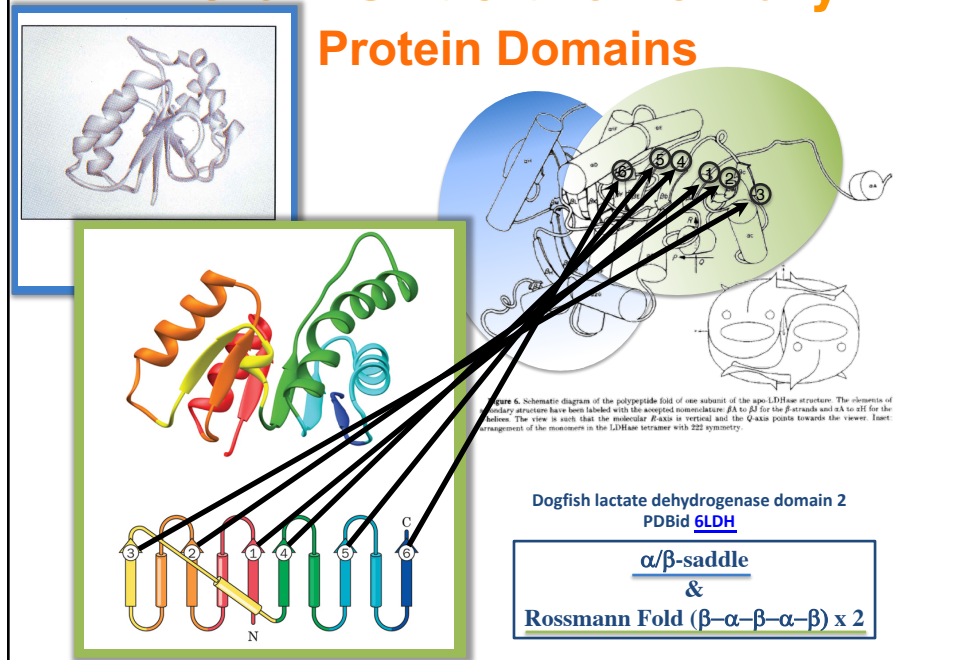
Recall:



Lactate dehydrogenase
domain 1

Protein Structure-Tertiary

Protein Domains



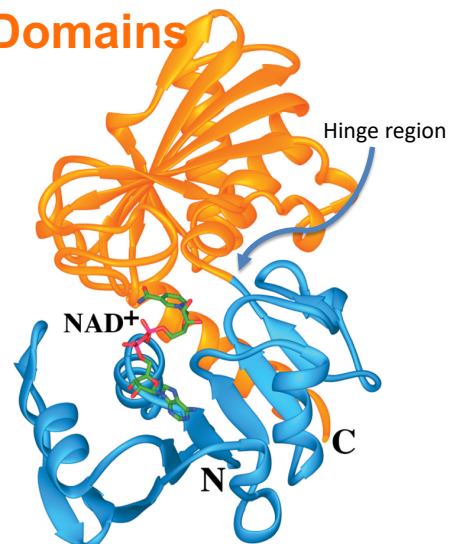
Protein Structure-Tertiary

Protein Domains

2-Domain Protein : GAPDH

Glyceraldehyde-3-phosphate
dehydrogenase
PDBid [1GD1](#)

α/β -saddle
&
Rossmann Fold (β - α - β - α - β)



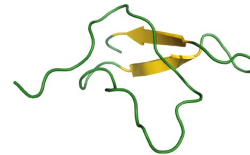
Based on an X-ray structure by Alan Wonacott, Imperial College, London, U.K. PDBid 1GD1.

Protein Structure-Tertiary

Intrinsically Disordered Proteins: Tachystatin

Unstructured domains:

Part of primary structure without any defined conformation, changeable, dynamic, several possible structures depending on binding partners in cells

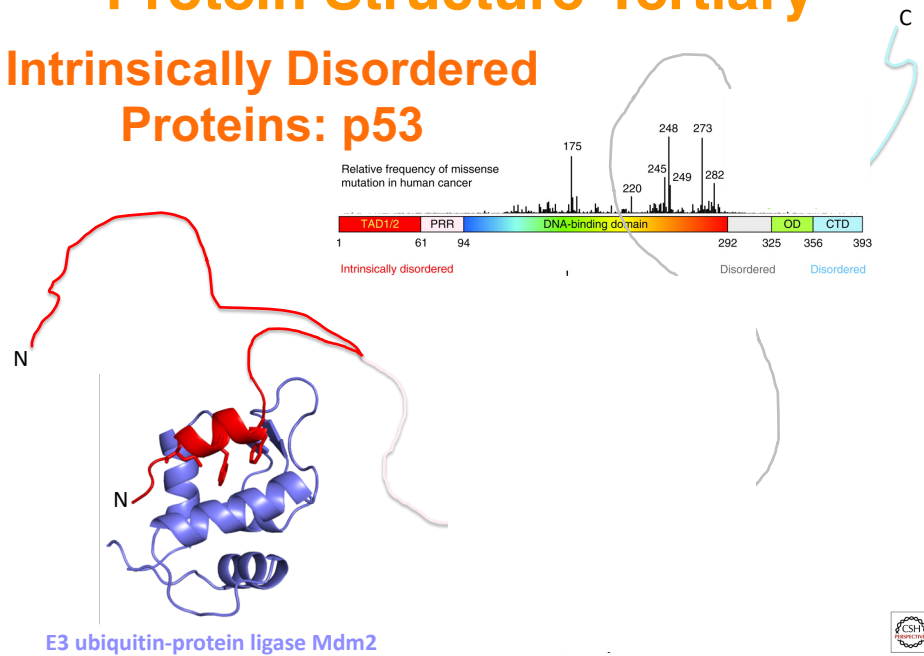


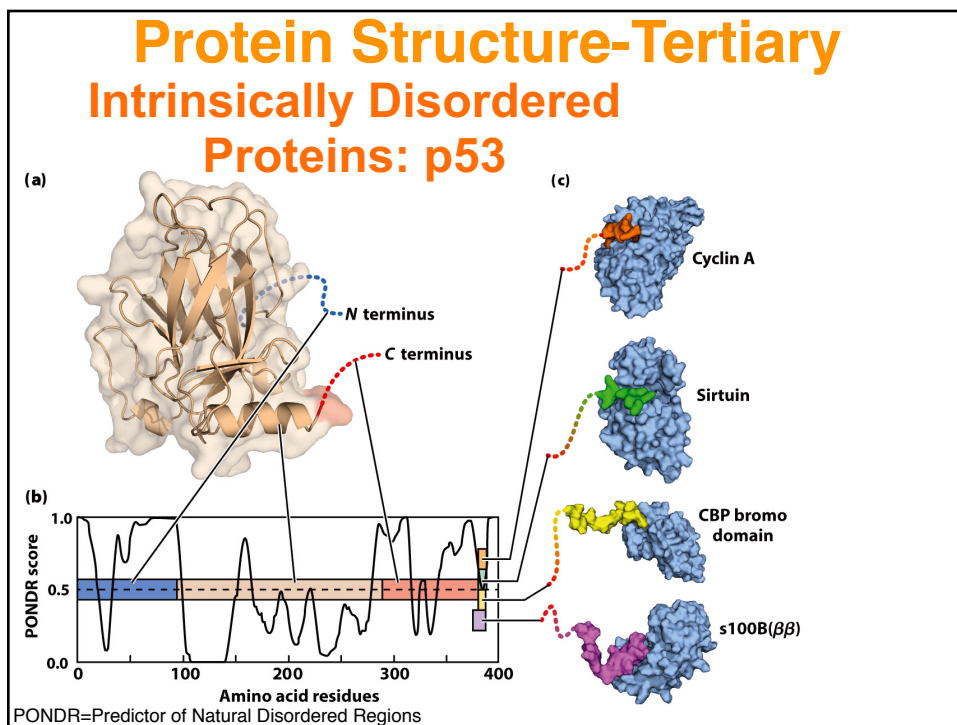
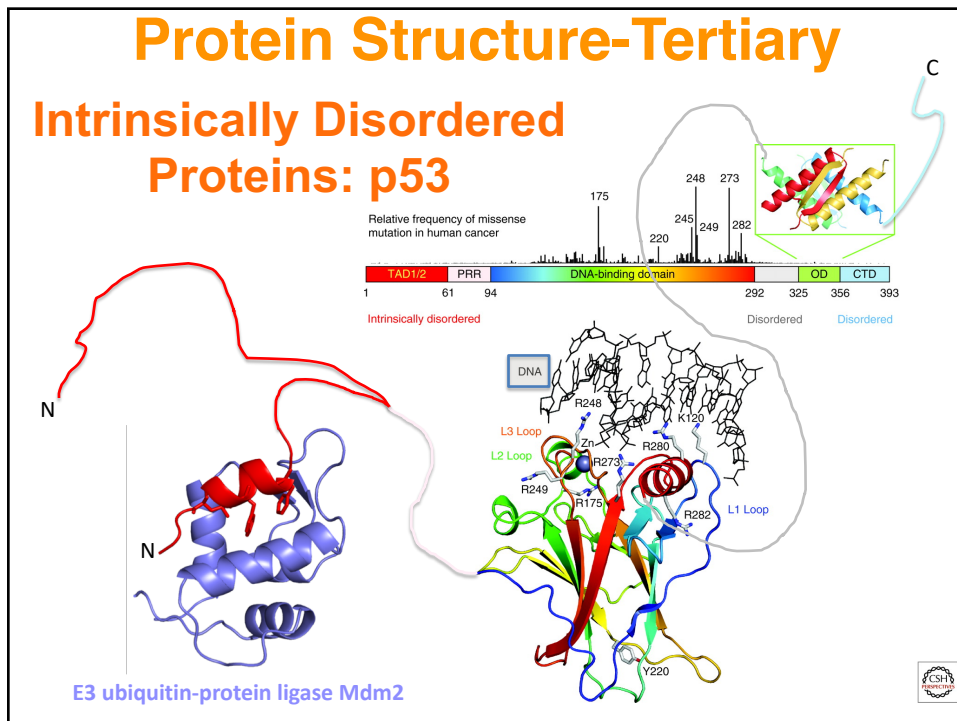
Tachystatin

20

Protein Structure-Tertiary

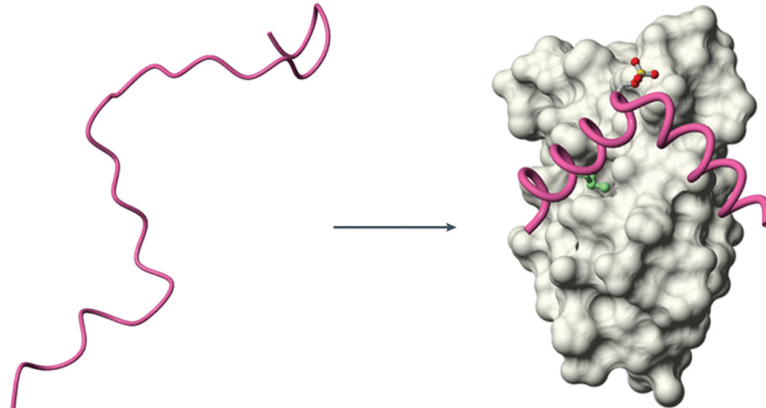
Intrinsically Disordered Proteins: p53





Protein Structure-Tertiary

Intrinsically Disordered Proteins: CREB

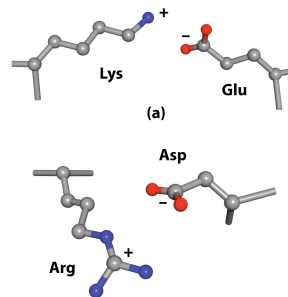
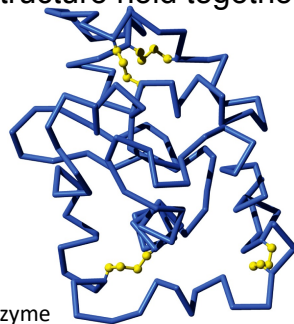


CREB (cAMP response element-binding protein)

Kinase-inducible domain of CBP
(CREB-binding protein)
PDBid [1KDX](#)

Protein Structure-Summary Tertiary

- 3° structure is a collection of 2° structures in motifs and/or domains
- Sum of weak interactions
- 3° structure held together with side-chain interactions



- Hydrophobic effect
- Hydrogen bonds
 - Disulfide bonds
- Salt bridges
- van der Waals (Dispersion forces)

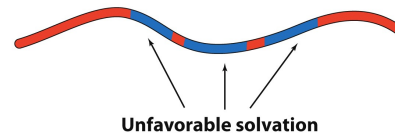
Protein Structure-Tertiary

Hydrophobic effect drives protein folding

(a) Folded



(b) Unfolded



Hydropathy Plot

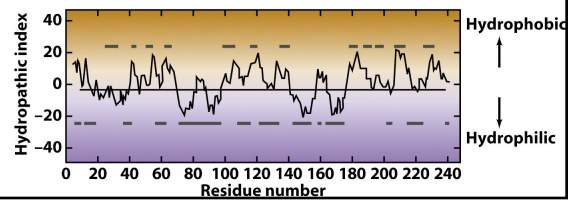


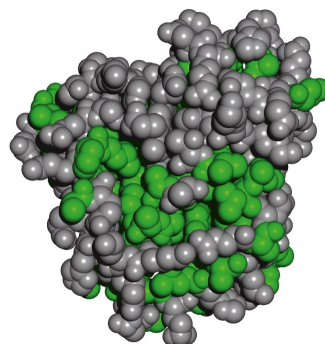
TABLE 4-3 Hydrophobicity Scales

Residue	Scale A*	Scale B*
Phe	2.8	3.7
Met	1.9	3.4
Ile	4.5	3.1
Leu	3.8	2.8
Val	4.2	2.6
Cys	2.5	2.0
Trp	-0.9	1.9
Ala	1.8	1.6
Thr	-0.7	1.2
Gly	-0.4	1.0
Ser	-0.8	0.6
Pro	-1.6	-0.2
Tyr	-1.3	-0.7
His	-3.2	-3.0
Gln	-3.5	-4.1
Asn	-3.5	-4.8
Glu	-3.5	-8.2
Lys	-3.9	-8.8
Asp	-3.5	-9.2
Arg	-4.5	-12.3

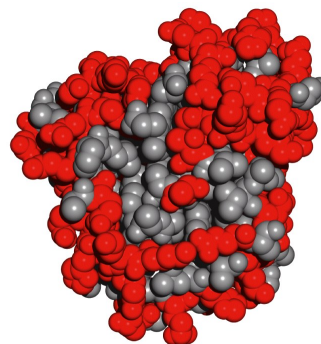
*Scale A is from Kyte, J., and Doolittle, R.F., *J. Mol. Biol.* 157, 105-132 (1982).
 *Scale B is from Engelman, D.M., Steitz, T.A., and Goldman, A., *Annu. Rev. Biophys. Chem.* 15, 321-353 (1986).

Protein Structure-Tertiary

Globular proteins



(a)



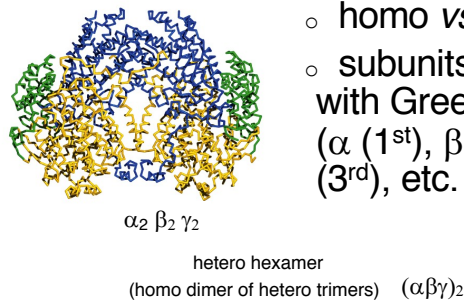
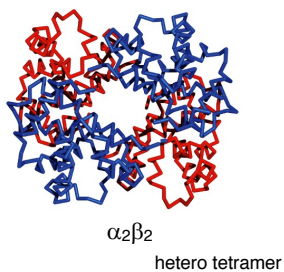
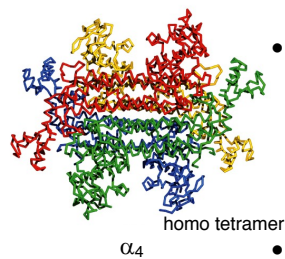
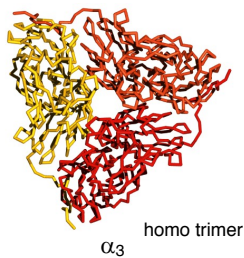
(b)

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- a hydrophobic core and a hydrophilic surface

Quaternary Structure

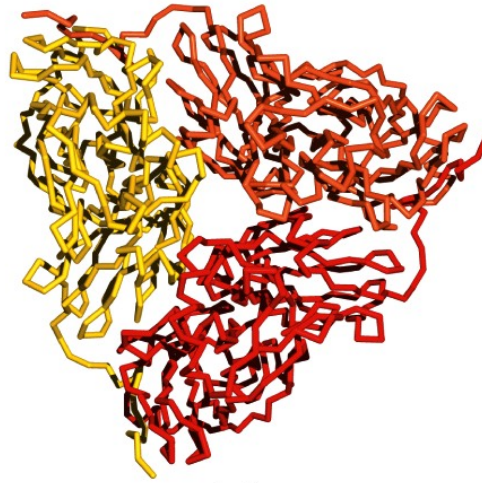
Protein Structure-Quaternary



- Multiple subunits held together by primarily non-covalent interactions
- Nomenclature:
 - homo vs. hetero
 - subunits indicated with Greek letters (α (1st), β (2nd), γ (3rd), etc.)

Protein Structure-Quaternary

Same weak interactions determine 4° structure

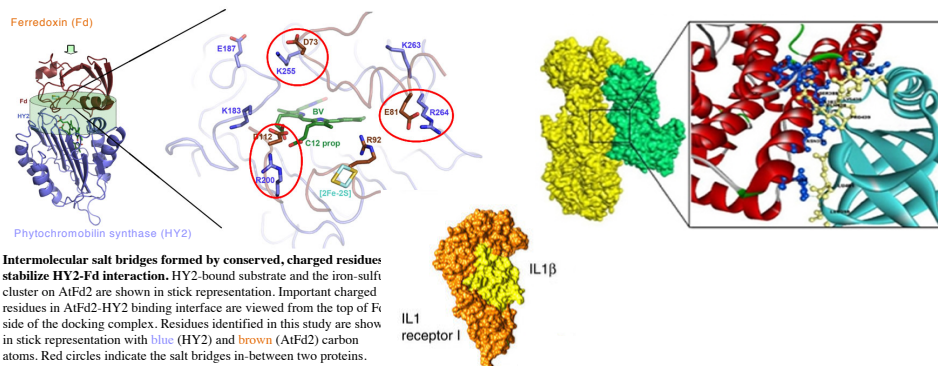


- Hydrophobic effect
- Hydrogen bonds
- Salt bridges
- van der Waals (Dispersion forces)

Protein Structure-Quaternary

4° structure held together with side-chain interactions

Sum of weak interactions



- Hydrophobic effect
- Hydrogen bonds
- Salt bridges
- van der Waals forces

Protein Structure-Summary

