Computational Systems Biology

Lecture 2: Enzymes

Images from: David L. Nelson, Lehninger Principles of Biochemistry, IV Edition, Freeman ed.
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Suggested reading

Book:
David L. Nelson, Lehninger - Principles of Biochemistry, 4th Edition (or 3rd Edition), W. H. Freeman ed.
http://bcs.whfreeman.com/lehninger/

- *Enzymes*
  - Lehninger Chapter 1.3 – Enzymes promote sequences of chemical reactions (pp 26-27)
  - Lehninger Chapter 3 – Amino acids, peptides and proteins (pp 75-89, for general reference)
  - Lehninger Chapter 6 – Enzymes (pp 190-200, for general reference)

(page numbers refer to the 4th edition)

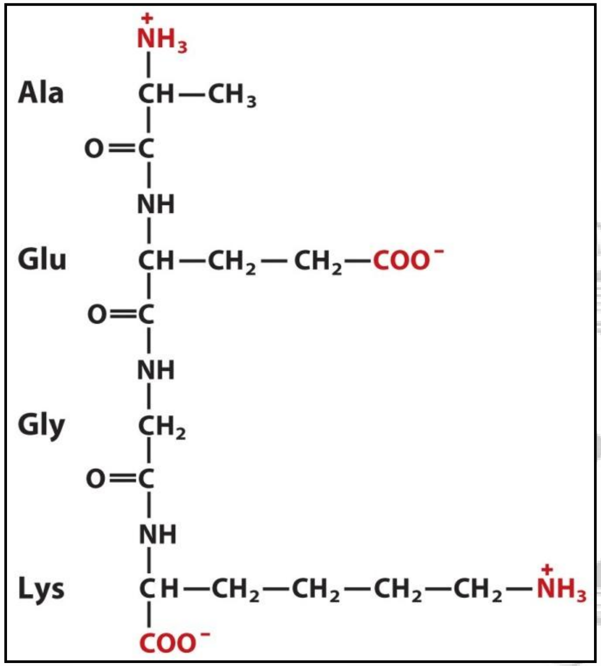
Summary

- What is an enzyme
- Enzymes 3D structures
- How enzyme work: enzymatic catalysis
- The Enzyme Classification (EC) codes

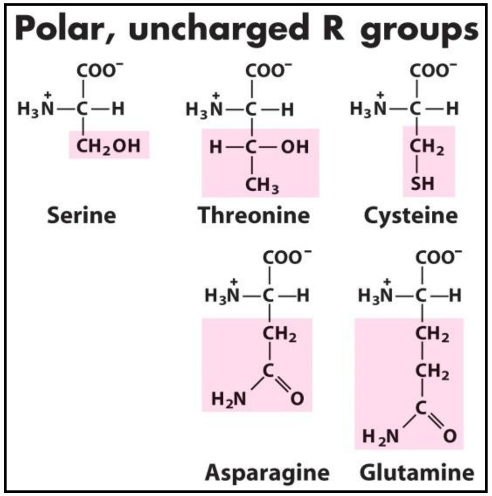
Enzymes are proteins

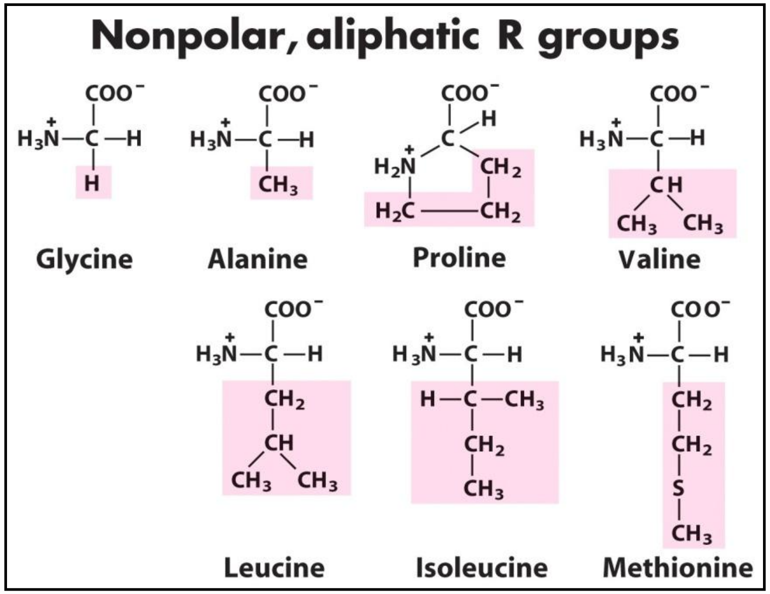
- In general, a protein is a chain of **amino acids** (aa) covalently linked (when the chain is short ~5-10 aa, the protein is often called oligopeptide/polypeptide or simply peptide)
- Thousands of different proteins are built with the same ubiquitous set of 20 amino acids (the protein “alphabet”)
- Some proteins have structural roles (e.g. actin in the muscles), other have catalytic (chemical-reaction-making) activity and are called **enzymes**

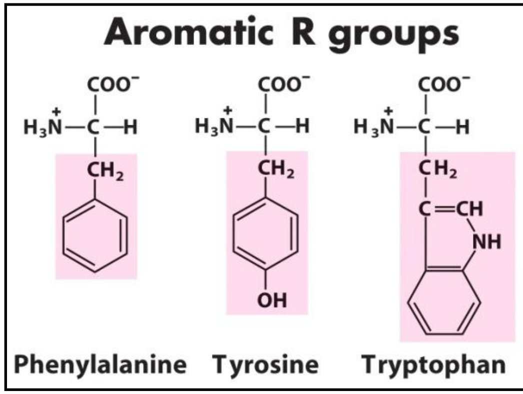
- A polypeptide with 4 amino acids (Ala-Glu-Gly-Lys)
- The electrically charged groups are shown in red
- In a longer protein the electrically charged lateral groups can line a pocket of the enzyme 3D structure to generate an active reaction site (see following slides)

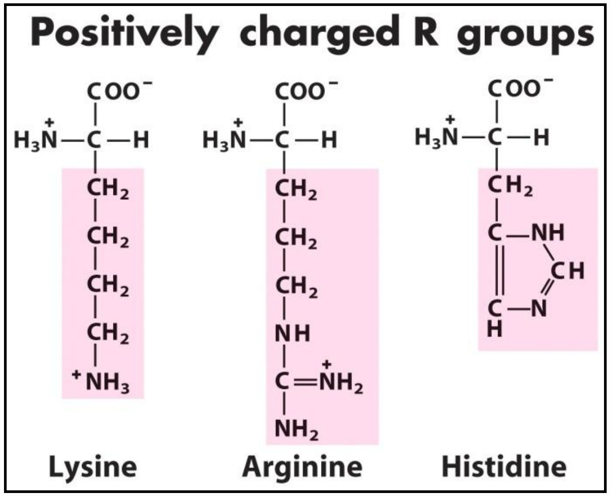


20 amino acids


Polar, uncharged R groups

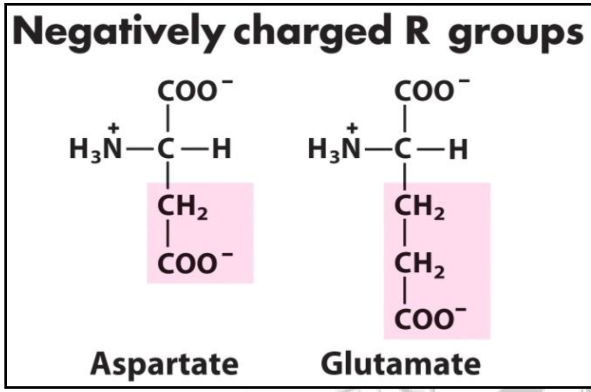

Nonpolar, aliphatic R groups


Aromatic R groups


Positively charged R groups

The 1 letter and 3 letters codes

G	Glycine	Gly	**P**	Proline	Pro
A	Alanine	Ala	**V**	Valine	Val
L	Leucine	Leu	**I**	Isoleucine	Ile
M	Methionine	Met	**C**	Cysteine	Cys
F	Phenylalanine	Phe	**Y**	Tyrosine	Tyr
W	Tryptophan	Trp	**H**	Histidine	His
K	Lysine	Lys	**R**	Arginine	Arg
Q	Glutamine	Gln	**N**	Asparagine	Asn
E	Glutamic Acid	Glu	**D**	Aspartic Acid	Asp
S	Serine	Ser	**T**	Threonine	Thr


Negatively charged R groups

Proteins come in all shapes and sizes

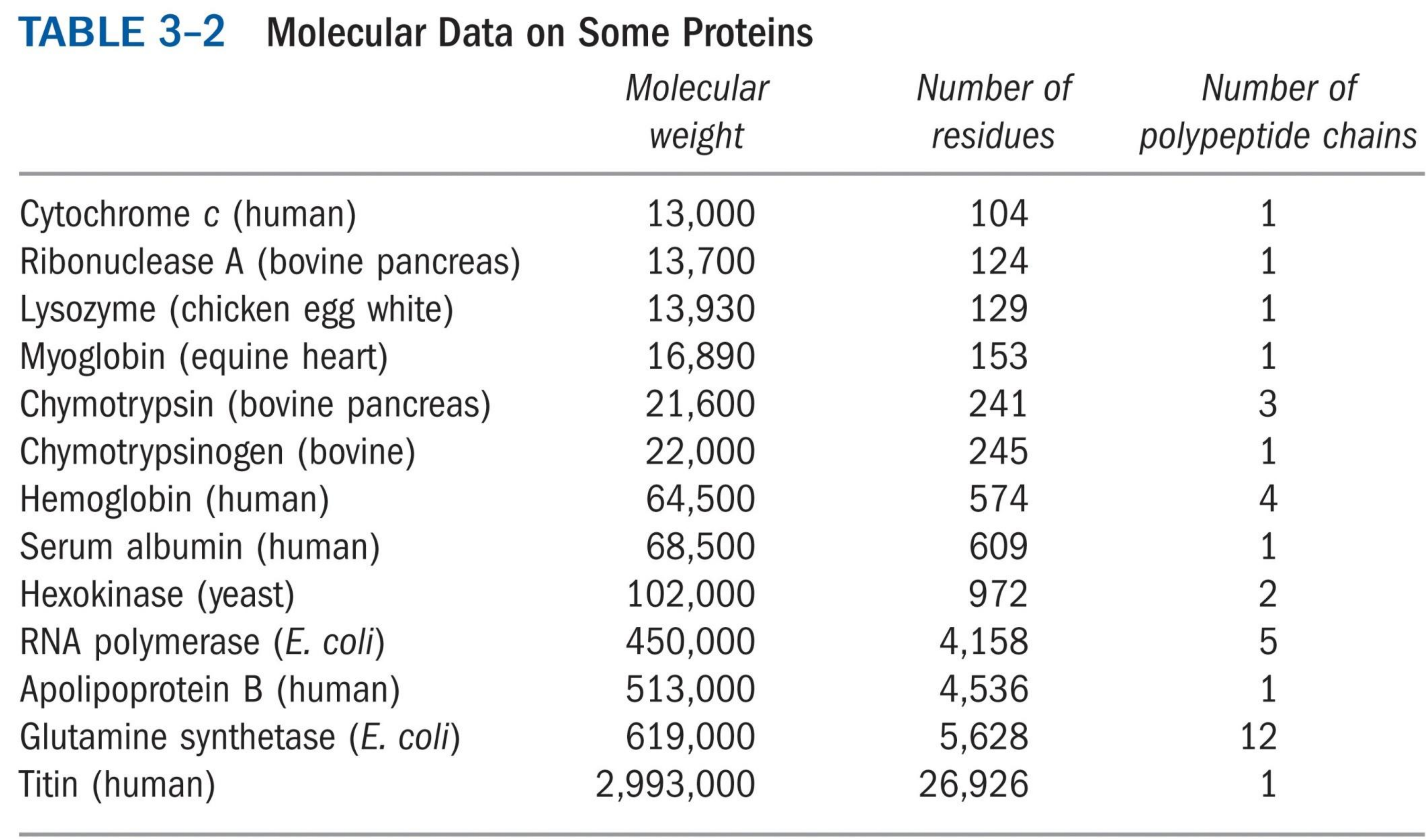
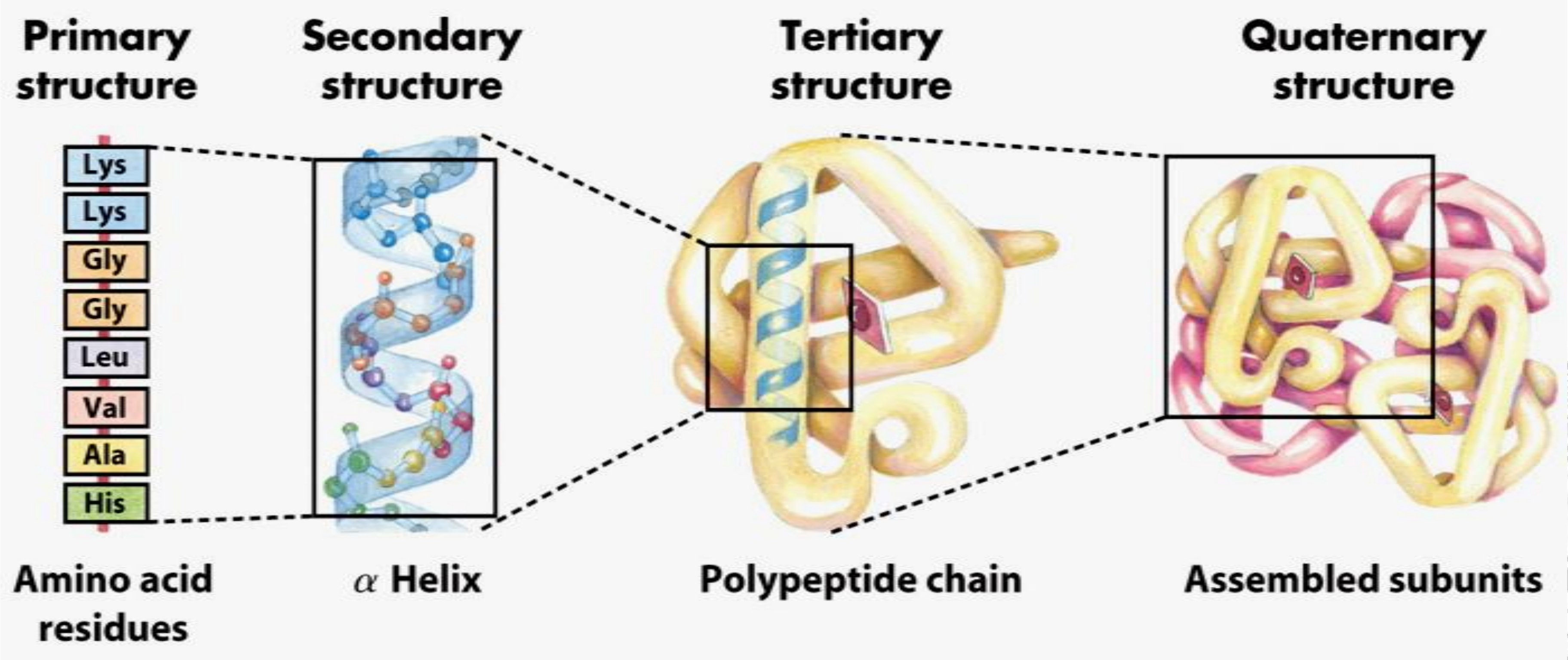


TABLE 3–2 Molecular Data on Some Proteins

	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

Enzymes 3D structure

- Enzymes are proteins and their activities depends on the 3D structure of the amino acids that compose them (note: also some RNAs have catalytic activity but they won't be covered in this course)



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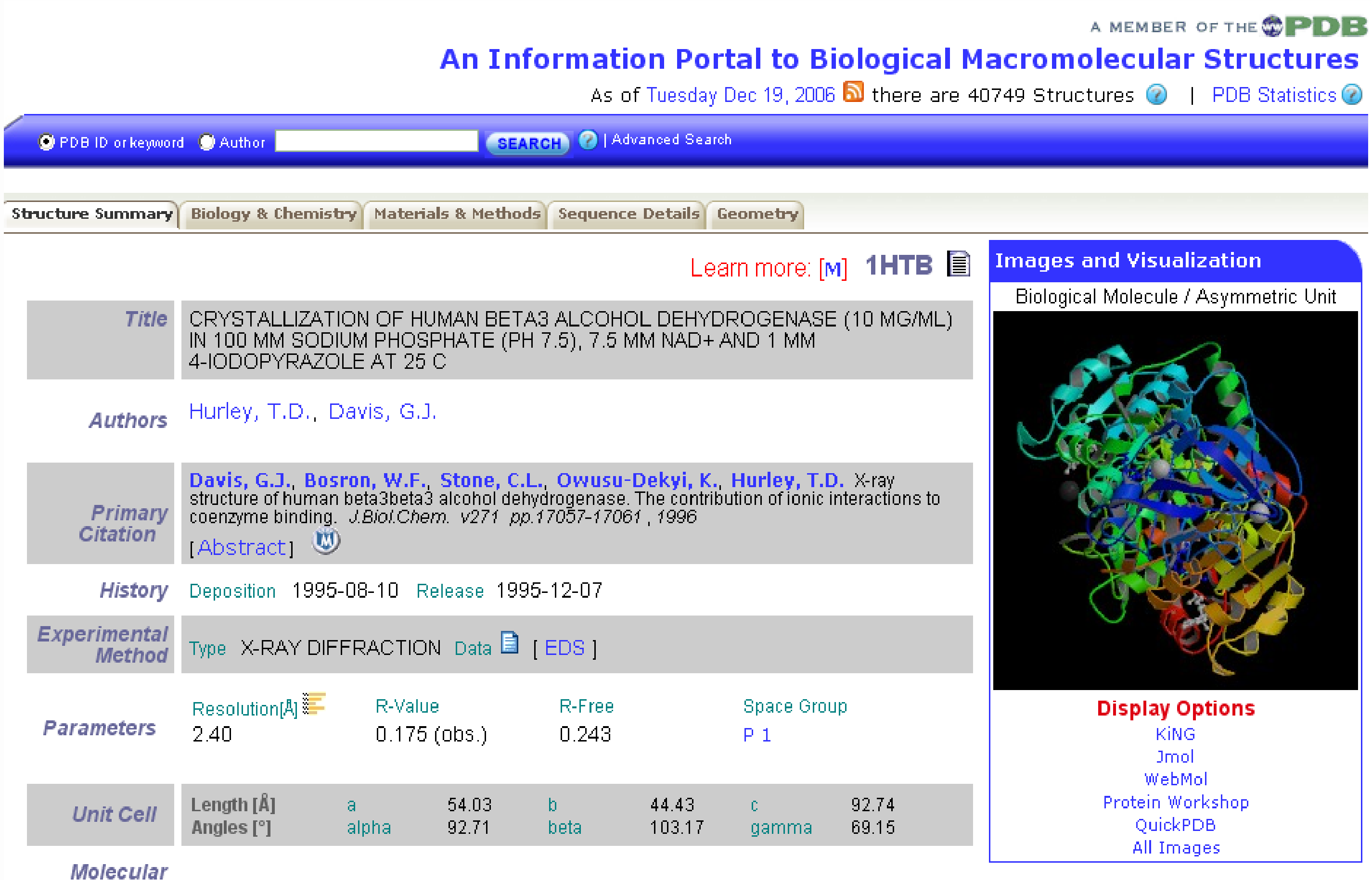
PDB - Database of protein structures

- PDB (RCSB Protein Data Bank)
- http://www.rcsb.org/pdb/home/home.do
- How is the data collected? Every 3D protein sequence has to be deposited in PDB before publication in reviewed journals



An Information Portal to Biological Macromolecular Structures

As of Tuesday Dec 19, 2006 there are 40749 Structures | PDB Statistics

Learn more: [M] **1HTB**

Title	CRYSTALLIZATION OF HUMAN BETA3 ALCOHOL DEHYDROGENASE (10 MG/ML) IN 100 MM SODIUM PHOSPHATE (PH 7.5), 7.5 MM NAD+ AND 1 MM 4-IODOPYRAZOLE AT 25 C
Authors	Hurley, T.D., Davis, G.J.
Primary Citation	**Davis, G.J., Bosron, W.F., Stone, C.L., Owusu-Dekyi, K., Hurley, T.D.** X-ray structure of human beta3beta3 alcohol dehydrogenase. The contribution of ionic interactions to coenzyme binding. *J.Biol.Chem. v271 pp.17057-17061 , 1996* [Abstract]
History	Deposition 1995-08-10 Release 1995-12-07
Experimental Method	Type X-RAY DIFFRACTION Data [EDS]

Parameters

Resolution[Å]	R-Value	R-Free	Space Group
2.40	0.175 (obs.)	0.243	P 1

Unit Cell

Length [Å]	a	54.03	b	44.43	c	92.74
Angles [°]	alpha	92.71	beta	103.17	gamma	69.15

Molecular

Images and Visualization

Biological Molecule / Asymmetric Unit

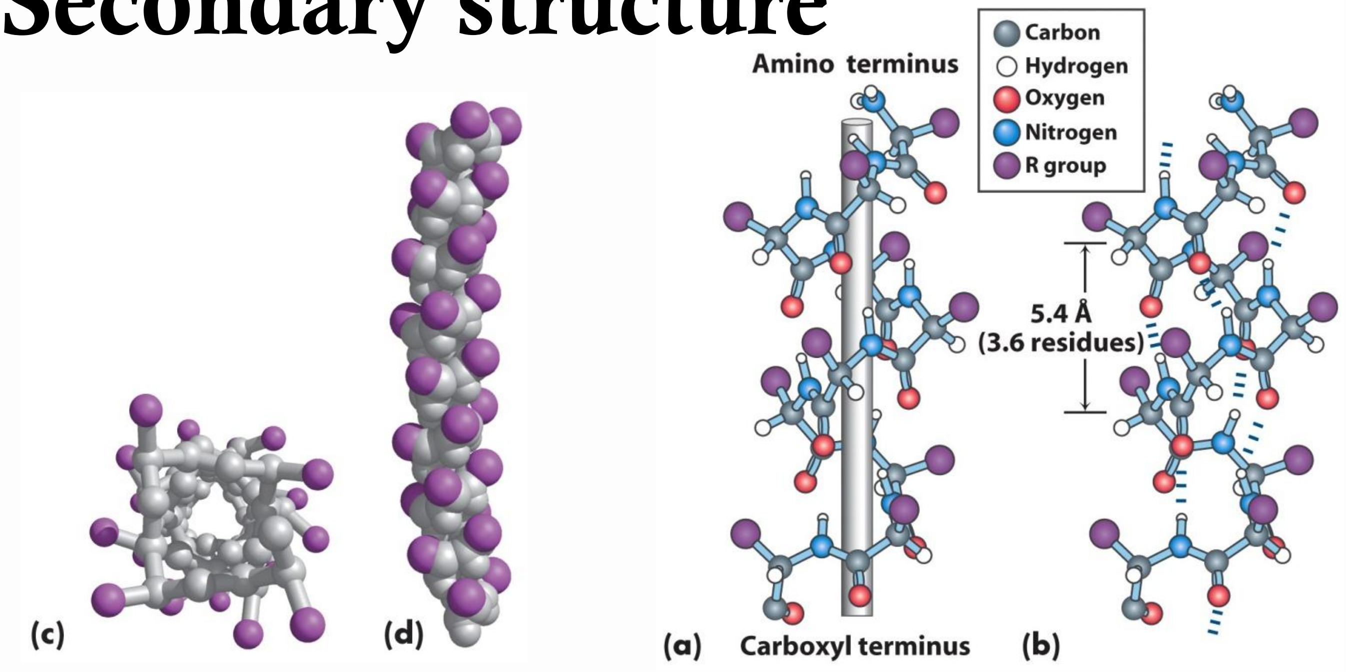
Display Options

KiNG
Jmol
WebMol
Protein Workshop
QuickPDB
All Images

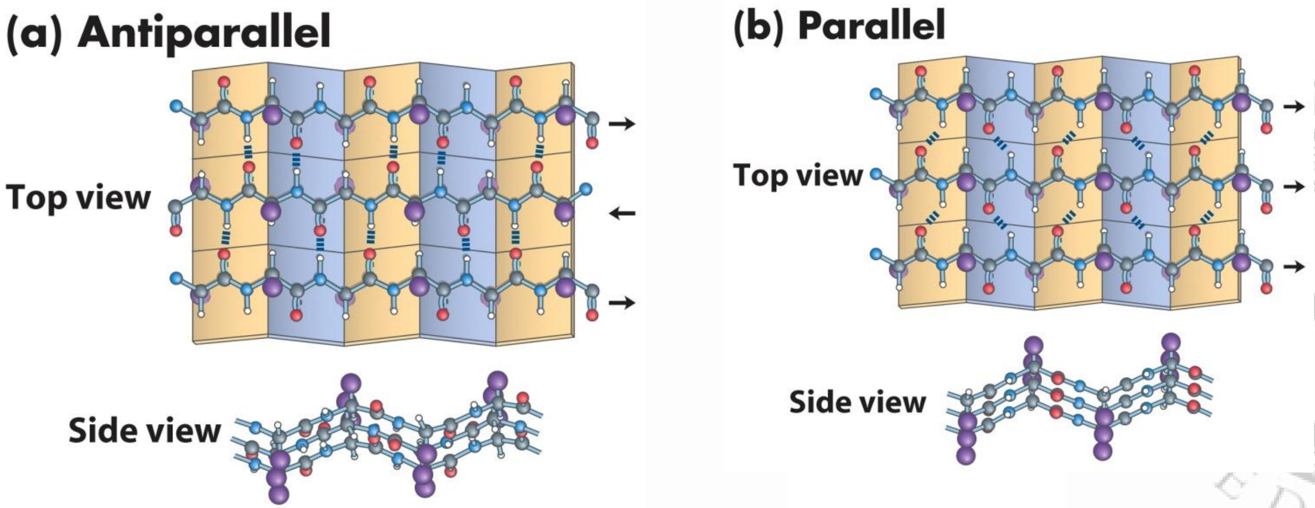
Secondary structure

- Common secondary structures are **alpha helixes**

(here in different graphical representations)

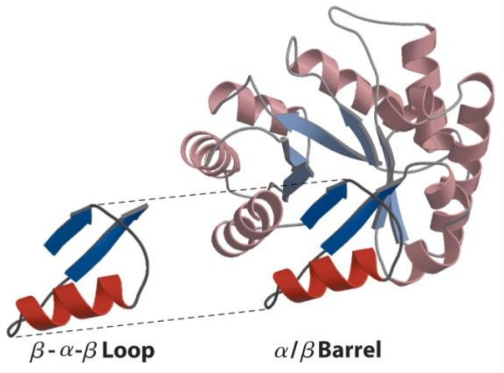


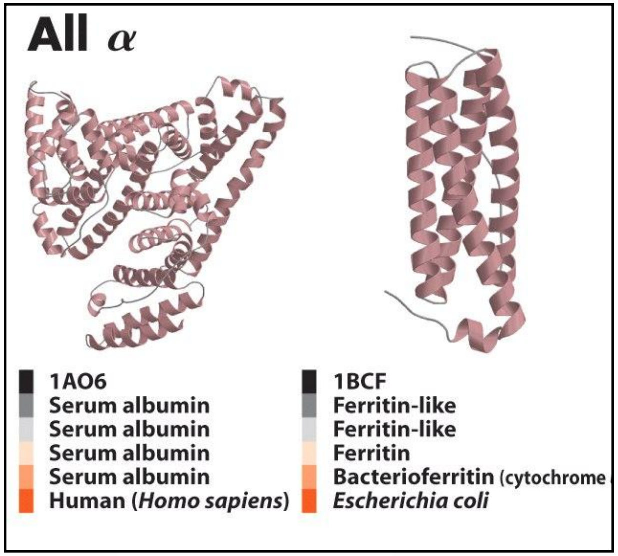
- And **beta sheets**



Structural domains

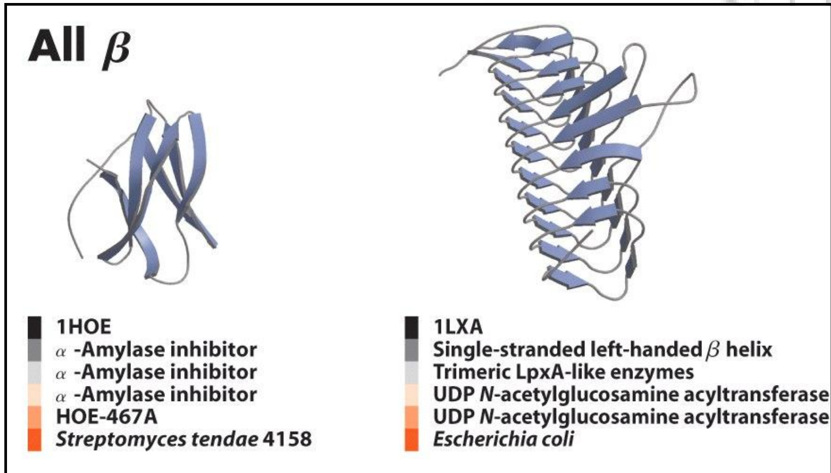
- Recurring **motifs** (here the beta-alpha-beta loop) are the basis for protein structural classification





- Enzymes with similar sequences and structural domains / motifs are classified in the same **protein family**

■ PDB identifier
■ Fold
■ Superfamily
■ Family
■ Protein
■ Species

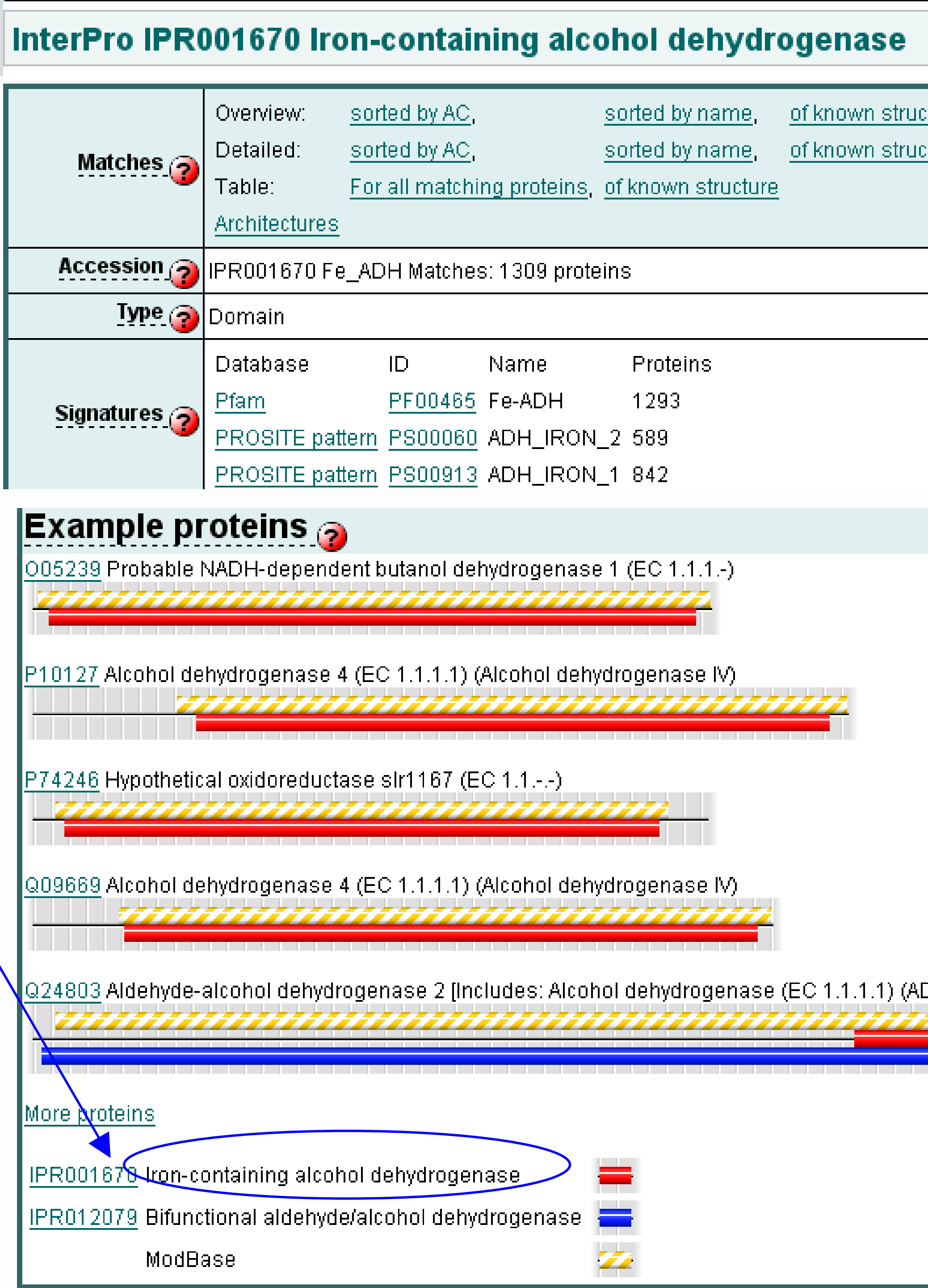


Interpro: the protein families database

- **InterPro** is a database of protein families, domains and functional sites

- Identifiable features found in known proteins can also be scanned against unknown protein sequences
- *(here an example of domain common to enzymes that use iron as cofactor to cut an hydrogen atom from an alcool).*

InterPro incorporates data from other databases



InterPro IPR001670 Iron-containing alcohol dehydrogenase

Matches	Overview: sorted by AC, sorted by name, of known struc Detailed: sorted by AC, sorted by name, of known struc Table: For all matching proteins, of known structure Architectures
Accession	IPR001670 Fe_ADH Matches: 1309 proteins
Type	Domain
Signatures	see below

Database	ID	Name	Proteins
Pfam	PF00465	Fe-ADH	1293
PROSITE pattern	PS00060	ADH_IRON_2	589
PROSITE pattern	PS00913	ADH_IRON_1	842

Example proteins

O05239 Probable NADH-dependent butanol dehydrogenase 1 (EC 1.1.1.-)

P10127 Alcohol dehydrogenase 4 (EC 1.1.1.1) (Alcohol dehydrogenase IV)

P74246 Hypothetical oxidoreductase slr1167 (EC 1.1.-.-)

Q09669 Alcohol dehydrogenase 4 (EC 1.1.1.1) (Alcohol dehydrogenase IV)

Q24803 Aldehyde-alcohol dehydrogenase 2 [Includes: Alcohol dehydrogenase (EC 1.1.1.1) (AD

More proteins

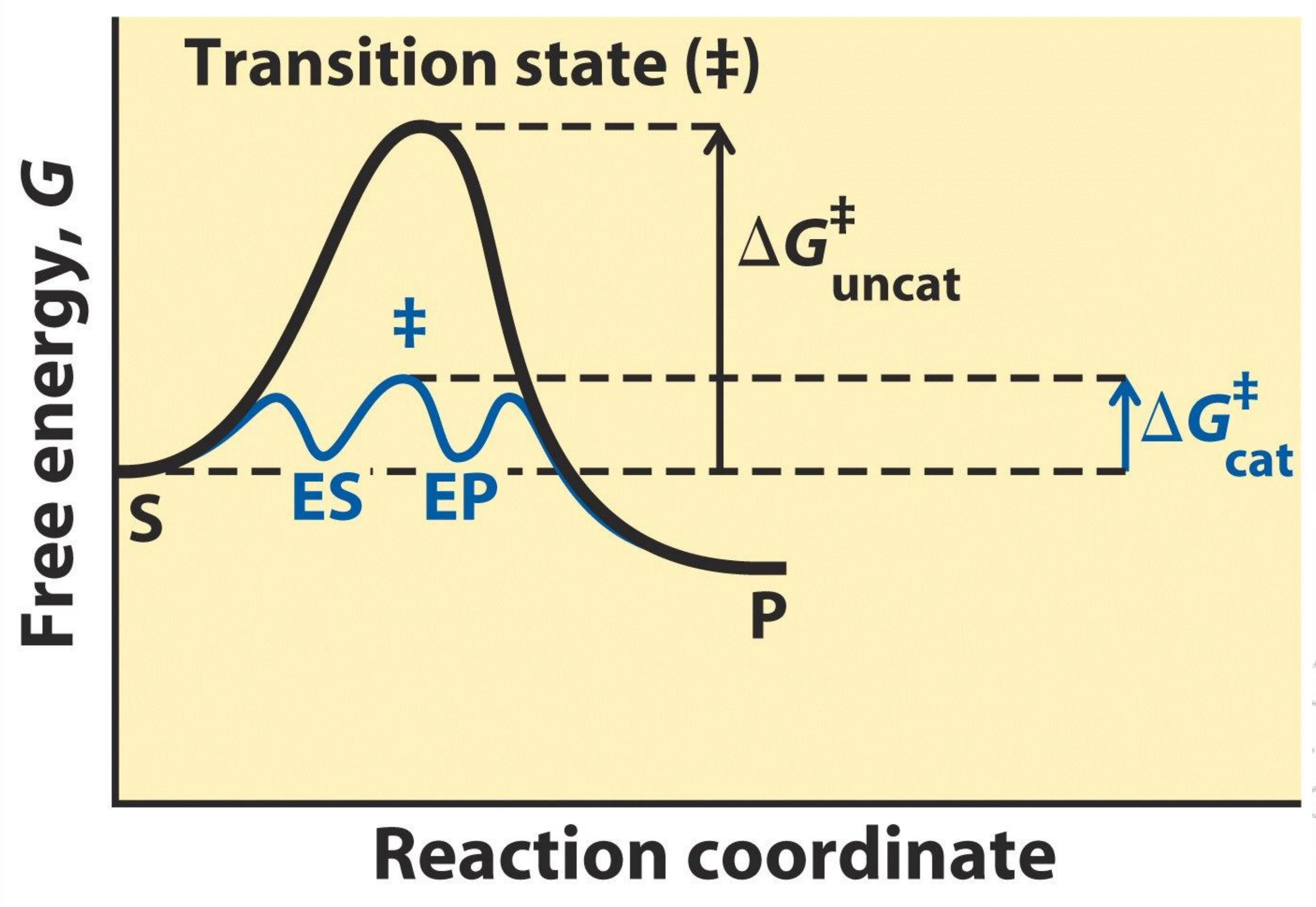
IPR001670 Iron-containing alcohol dehydrogenase 🟥
IPR012079 Bifunctional aldehyde/alcohol dehydrogenase 🟦
ModBase ▨

How enzymes work

- ***IMPORTANT:*** enzymes **do NOT** and **cannot** affect the equilibrium / free energy difference of a reaction

- Enzymes enhance the reaction rates (molecules produced per second) by lowering the activation energy of the transition state $\Delta G^{\ddagger}_{\mathbf{cat}}$

Transition state energy changed by an enzyme (in blue)



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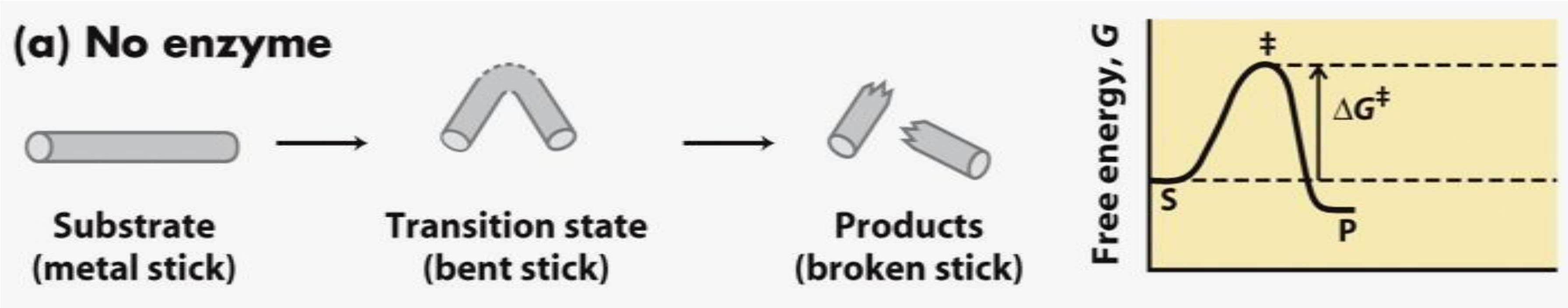
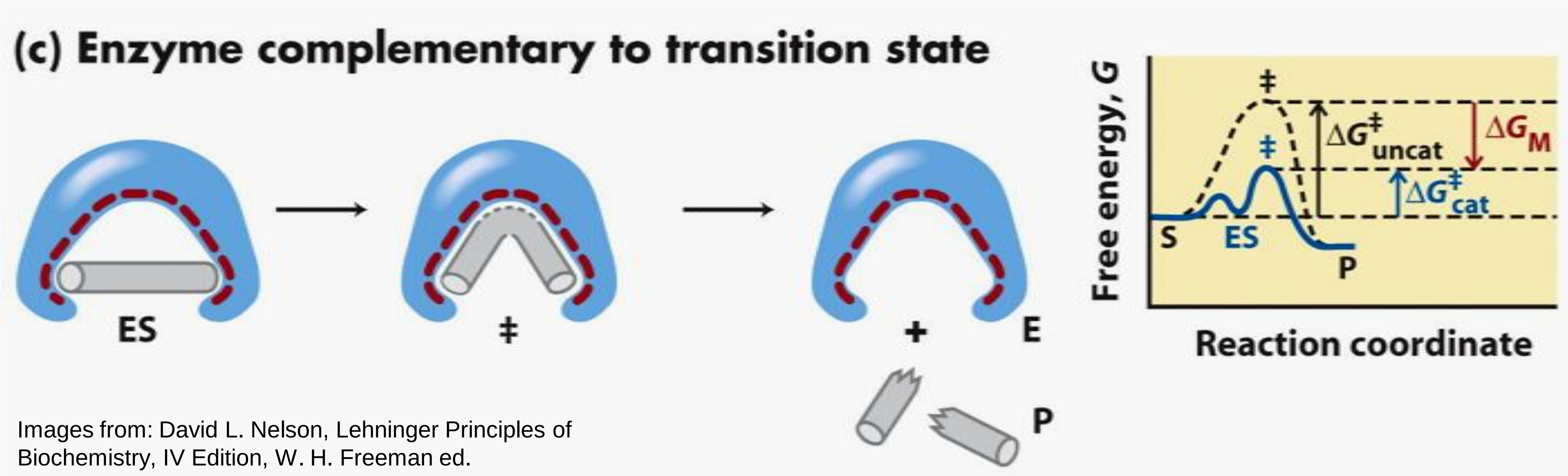
The enzyme action on the transition state



(a) No enzyme

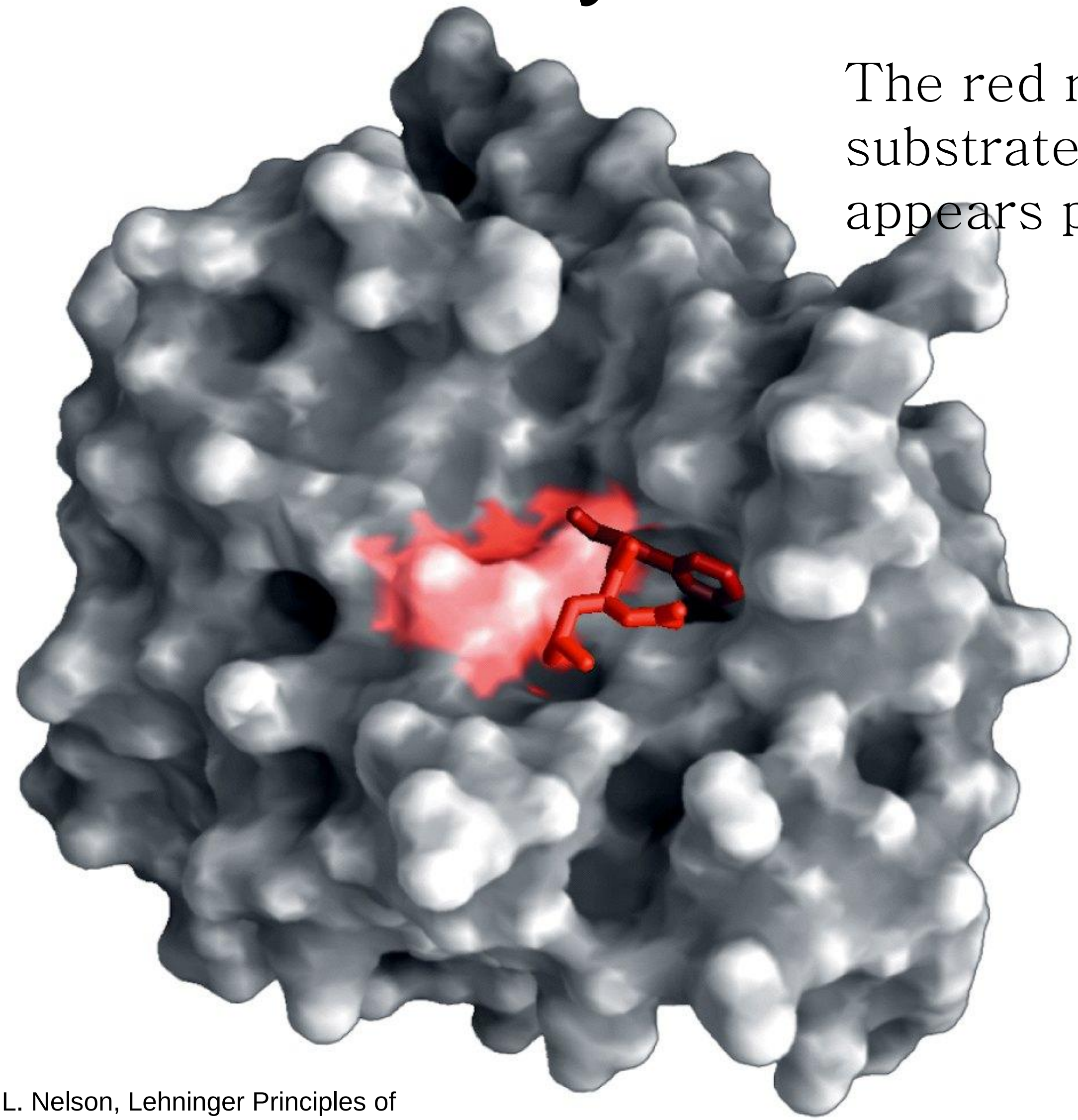


(c) Enzyme complementary to transition state

Images from: David L. Nelson, Lehninger Principles of Biochemistry, IV Edition, W. H. Freeman ed.

The enzyme active site

The red molecule is the substrate, the active site appears painted in red



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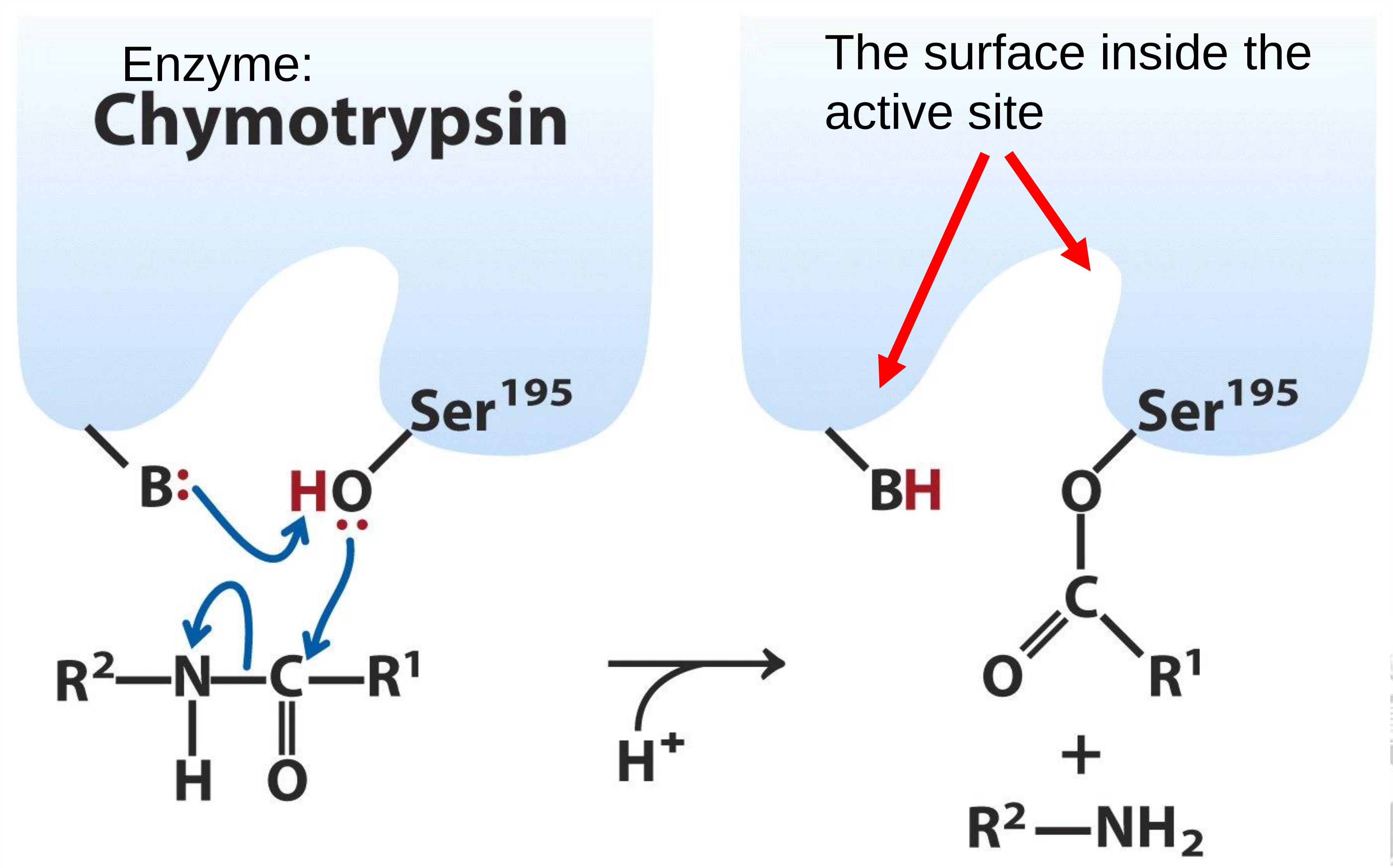

Enzyme:
Chymotrypsin

The surface inside the active site

You can see a flash demo of this enzymatic reaction on:
http://bcs.whfreeman.com/lehninger/ clicking on → Chapter 6: Enzymes → mechanism animation → fig 6.21 mechanism for chymotrypsin

Images from: David L. Nelson, Lehninger Principles of Biochemistry, IV Edition, W. H. Freeman ed.

E.C. Enzyme nomenclature

- Enzymes are named depending on the reaction they catalyse.

- Examples of enzyme groups are:
  - EC 1 - Oxidoreductases
  - EC 2 - Transferases
  - EC 3 - Hydrolases
  - EC 4 - Lyases
  - EC 5 - Isomerases
  - EC 6 - Ligases

An example of E.C. enzyme nomenclature

EC 3. Hydrolases

- EC 3.1 Hydrolases Acting on Ester Bonds
  - EC 3.1.3 Phosphoric Monoester Hydrolases
    - EC 3.1.3.1 alkaline phosphatase
    - EC 3.1.3.2 acid phosphatase
    - EC 3.1.3.3 phosphoserine phosphatase
    - EC 3.1.3.4 phosphatidate phosphatase
    - EC 3.1.3.5 5'-nucleotidase
    - EC 3.1.3.6 3'-nucleotidase
    - EC 3.1.3.7 3'(2'),5'-bisphosphate nucleotidase
    - EC 3.1.3.8 3-phytase
    - EC 3.1.3.9 glucose-6-phosphatase
    - EC 3.1.3.10 glucose-1-phosphatase
    - **EC 3.1.3.11 fructose-bisphosphatase**

Example: fructose-bisphosphatase EC 3.1.3.11

From the IUBMB (International Union of Biochemistry and Molecular Biology) web site:
http://www.chem.qmul.ac.uk/iubmb/enzyme/

one can reach a record for the enzyme: EC 3.1.3.11 (fructose-bisphosphatase):
http://www.chem.qmul.ac.uk/iubmb/enzyme/EC3/1/3/11.html

The site also contains the reaction diagram shown here:
http://www.chem.qmul.ac.uk/iubmb/enzyme/reaction/polysacc/Calvin2.html

The reaction involves the hydrolysis (separation) of a phosphate group here represented by **P_i**

The “P” representing the phosphate group that appears on the top region of the D-fructose-1,6-biphosphate substrate molecule has disappeared after the reaction, and the product is now called D-fructose 6-phospate (the phosphate group in position 1 is no more there).