

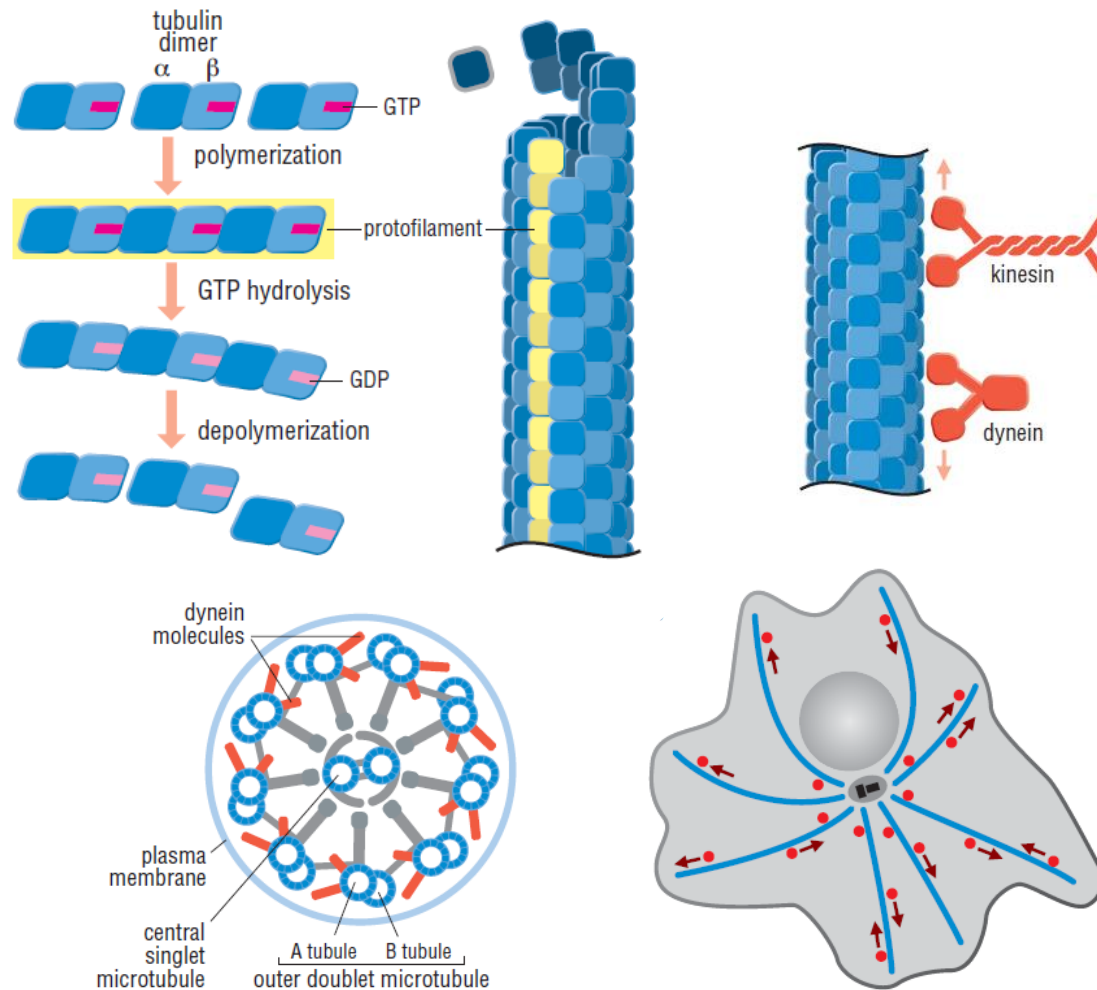
# FUNCTIONAL SITES IN PROTEIN STRUCTURES

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**Dr. Zhiyi Wei**  
SUSTC

# The three-dimensional structure of a protein determines its function

- We are focusing on biochemical function



# Molecular recognition

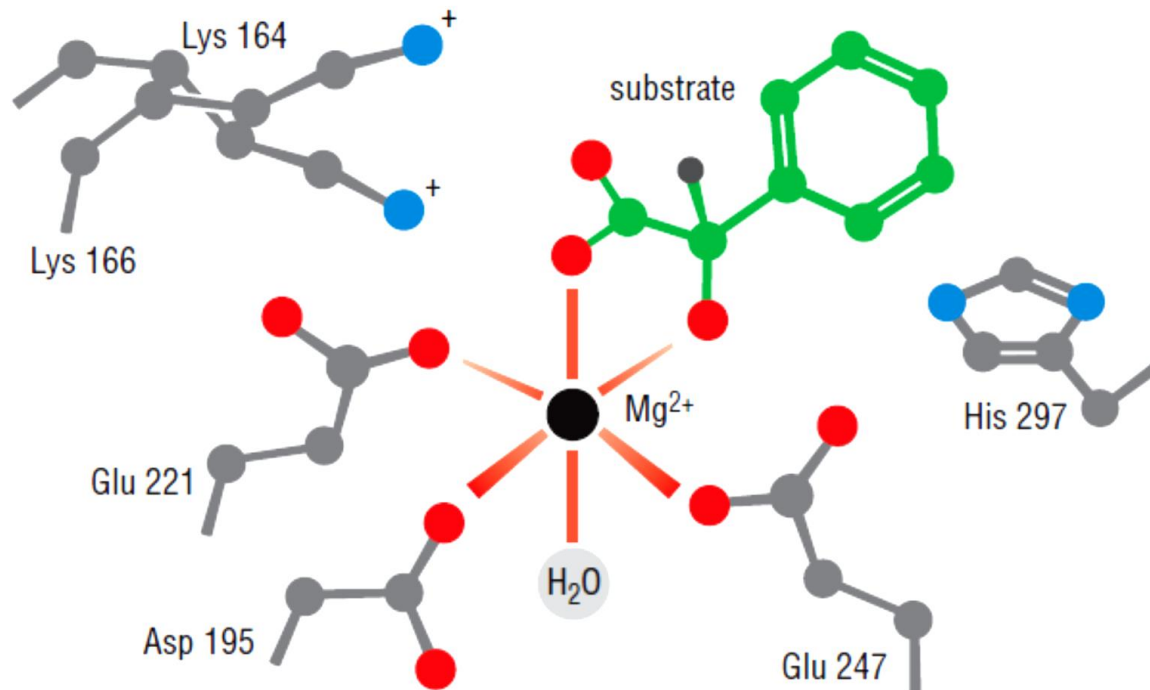
- Almost everything in your body can be recognized by proteins
  - Macromolecules or large assembly
    - DNA/RNA, protein, glycan, lipid bilayer
  - Small molecules
    - Nucleotide (like ATP), ion (like  $\text{Ca}^{2+}$ ), various organic chemicals (like Heme and vitamin), water, gas, or even proton.
- The functions of all proteins depend on the ability to bind ligands
  - Nomenclature of ligand (in my class hereafter): refers to those interacting molecules other than proteins
- Recognition features of proteins
  - High specificity
  - Can be versatile or selective
- Recognition is achieved by complementary binding
  - Complementarity of shape
  - Complementarity of weak interactions

# Functional Site

- Protein structures provide **specialized microenvironments** for molecular recognition
  - **Binding site**
  - **Active site** (involved in catalysis)
- The microscopic environment of the site
  - Usually a cavity, pocket, or cleft
  - Providing a different chemical environment from the bulk solution around the protein
    - Hydrophobic for hydrophobic ligand or protein
    - Charged for reverse-charged ligand or protein

# Active Site

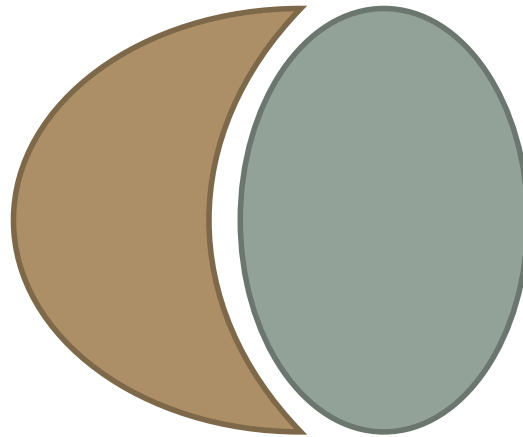
- Asymmetric pocket on or near the surface of a macromolecule that promotes chemical catalysis when the appropriate substrate binds
  - Creating an environment which is very difficult to achieve in free solution
- General acid-base catalysis
  - Protons are transferred between donating or accepting atoms on the substrate and key basic and acidic side chains



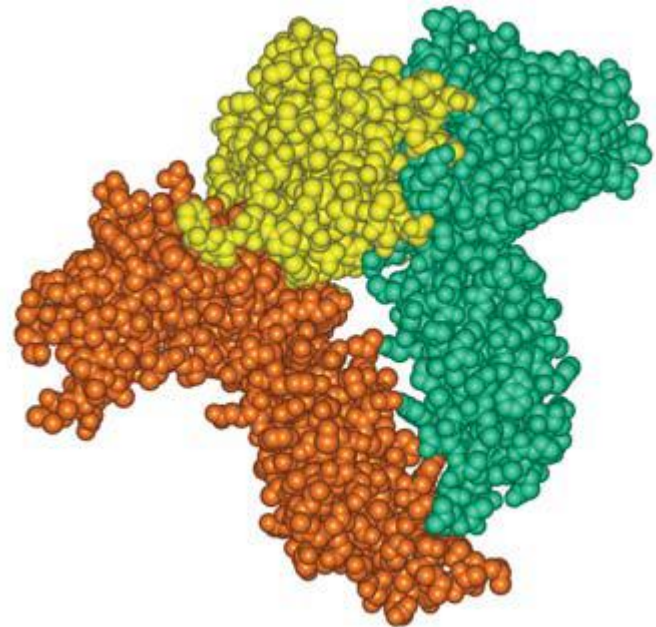
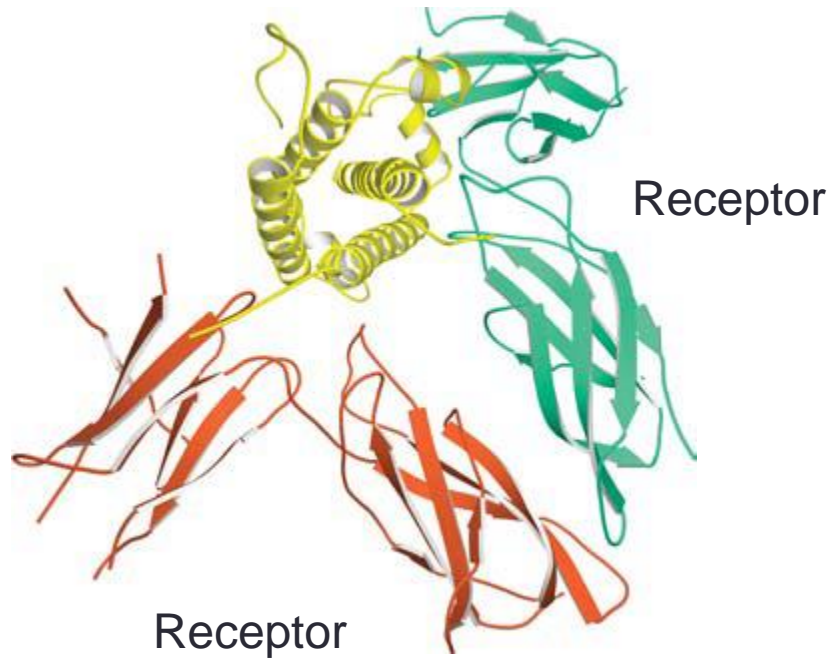
The active site of mandelate racemase

# Location of binding sites

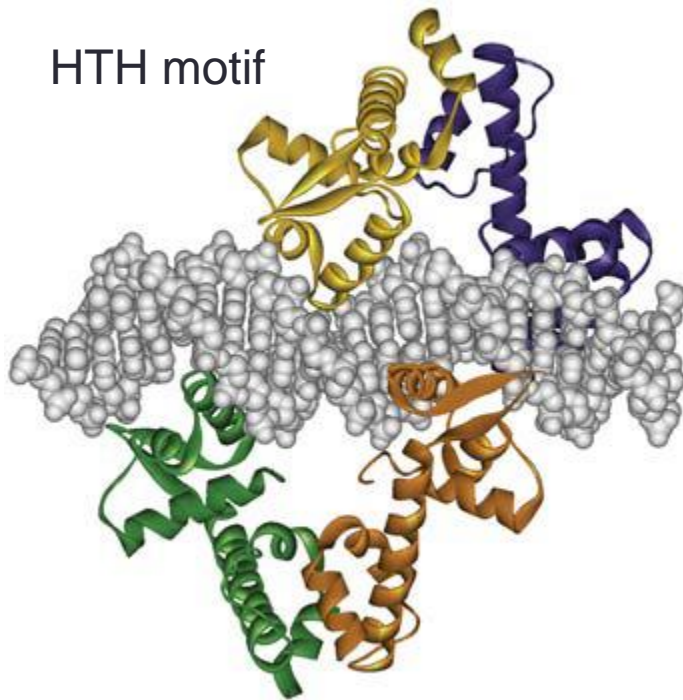
- Binding sites for macromolecules on a protein's surface can be concave, convex, or flat



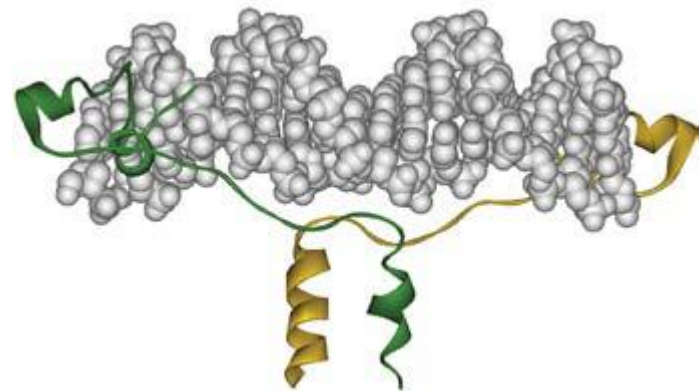
Growth hormone



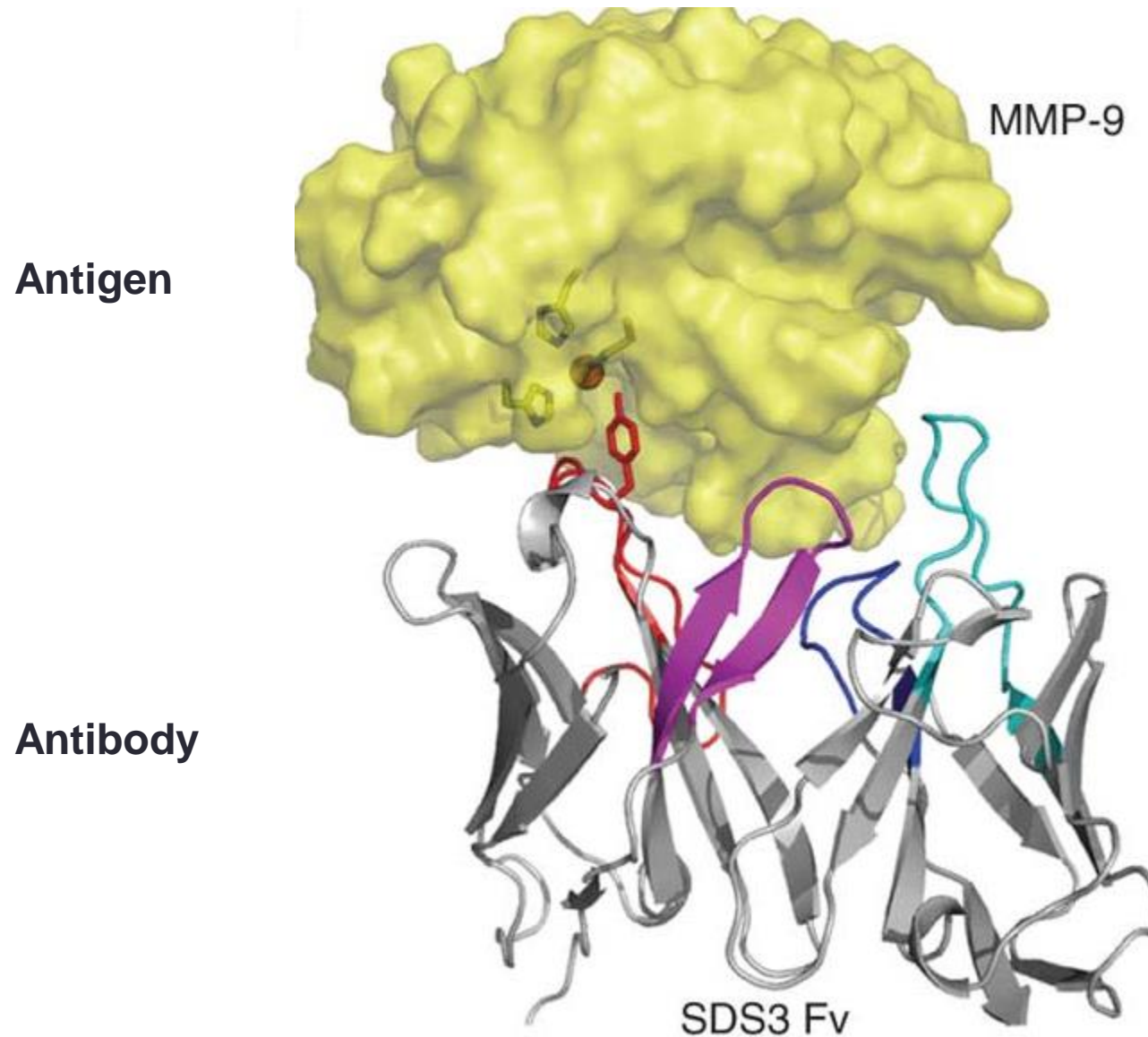
HTH motif



Zinc finger

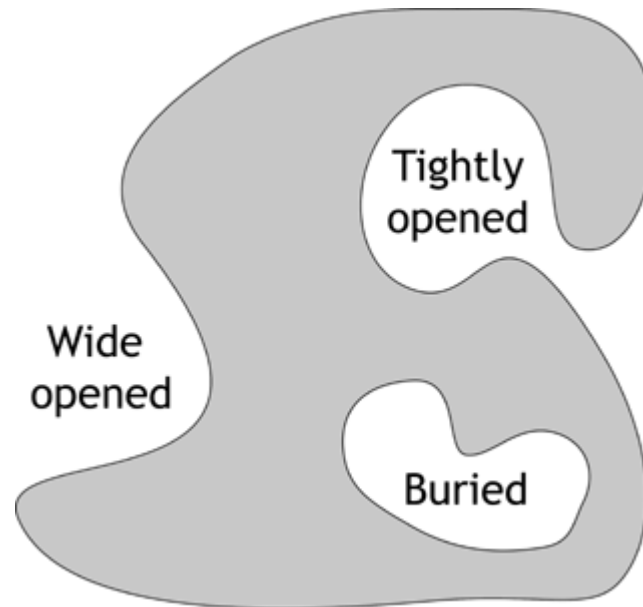


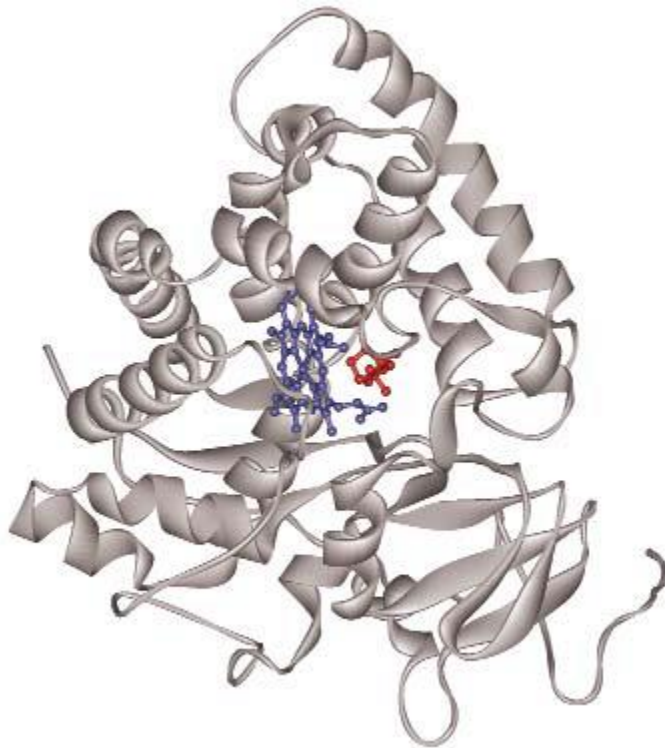




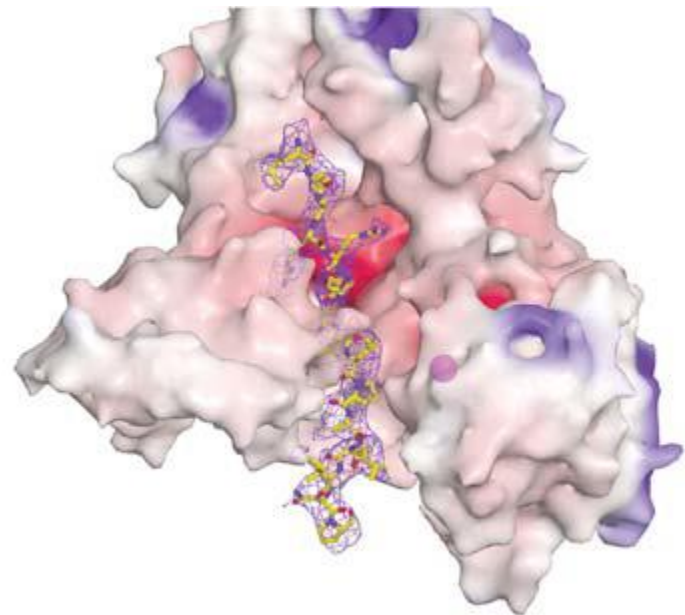
# Location of binding sites

- Binding sites for small ligands are clefts, pockets or cavities

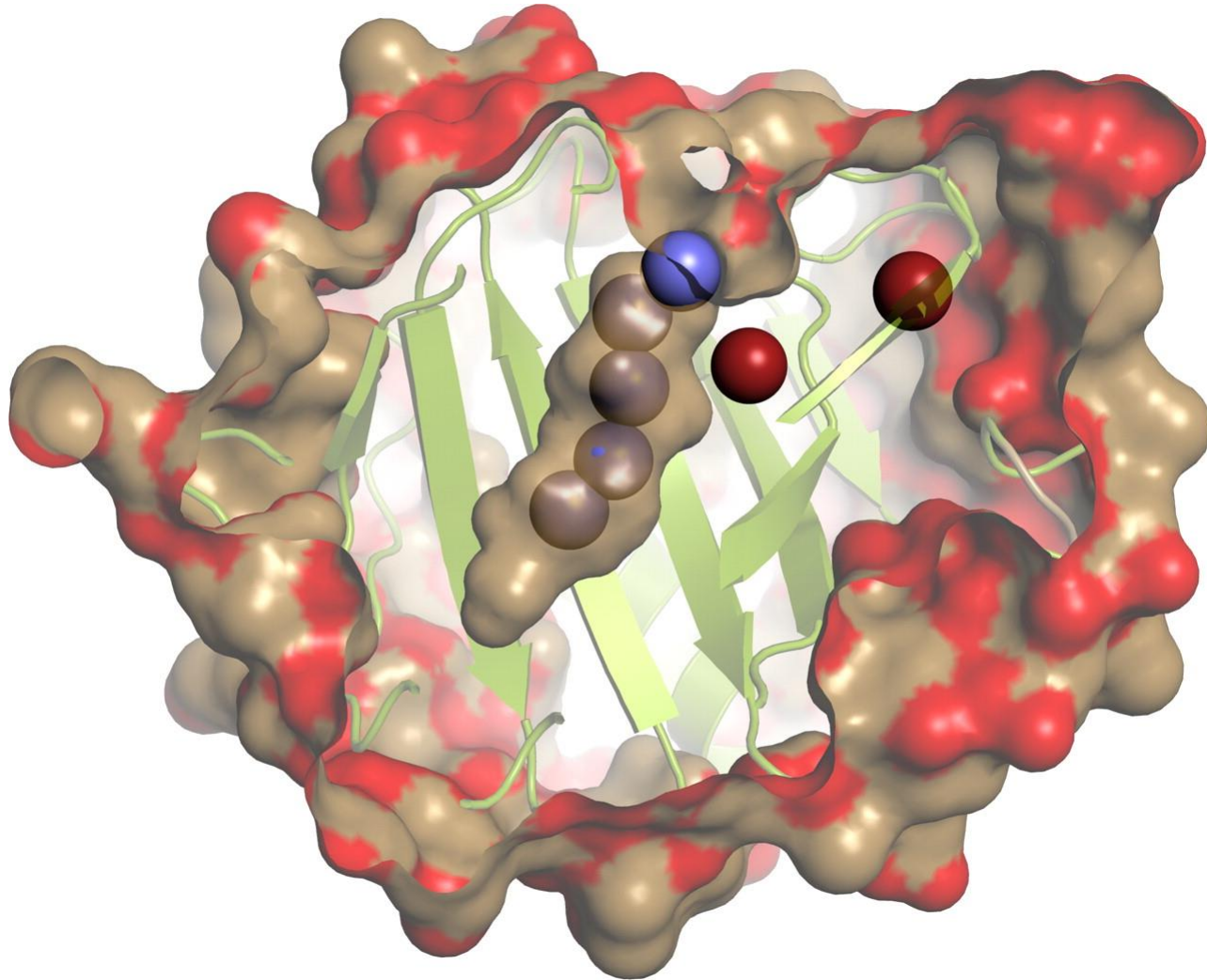




bacterial cytochrome P450 with its  
substrate camphor bound



Substrate binding to anthrax  
toxin lethal factor

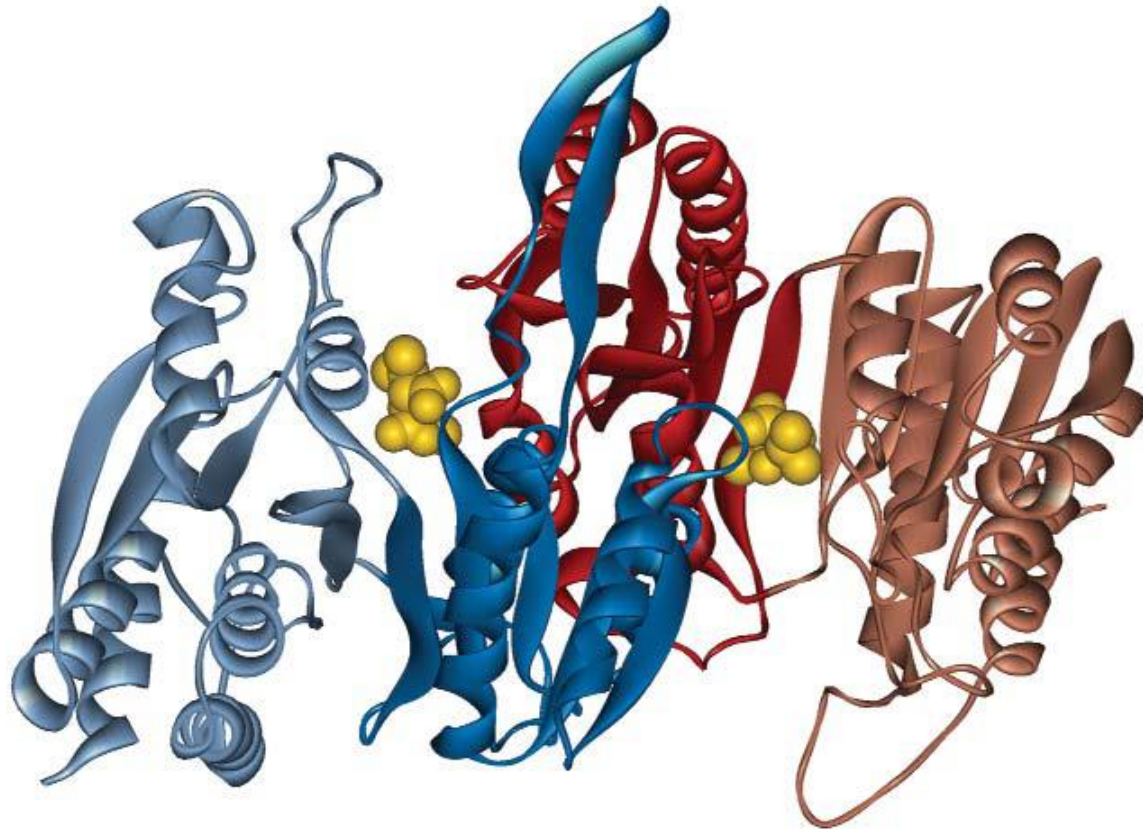


$\beta$ -lactoglobulin (PDB 3BLG), showing two water molecules (red) buried in small polar cavities and five water molecules (blue) modeled in the nonpolar calyx.

Qvist, et al. PNAS (2008)

# Location of active sites

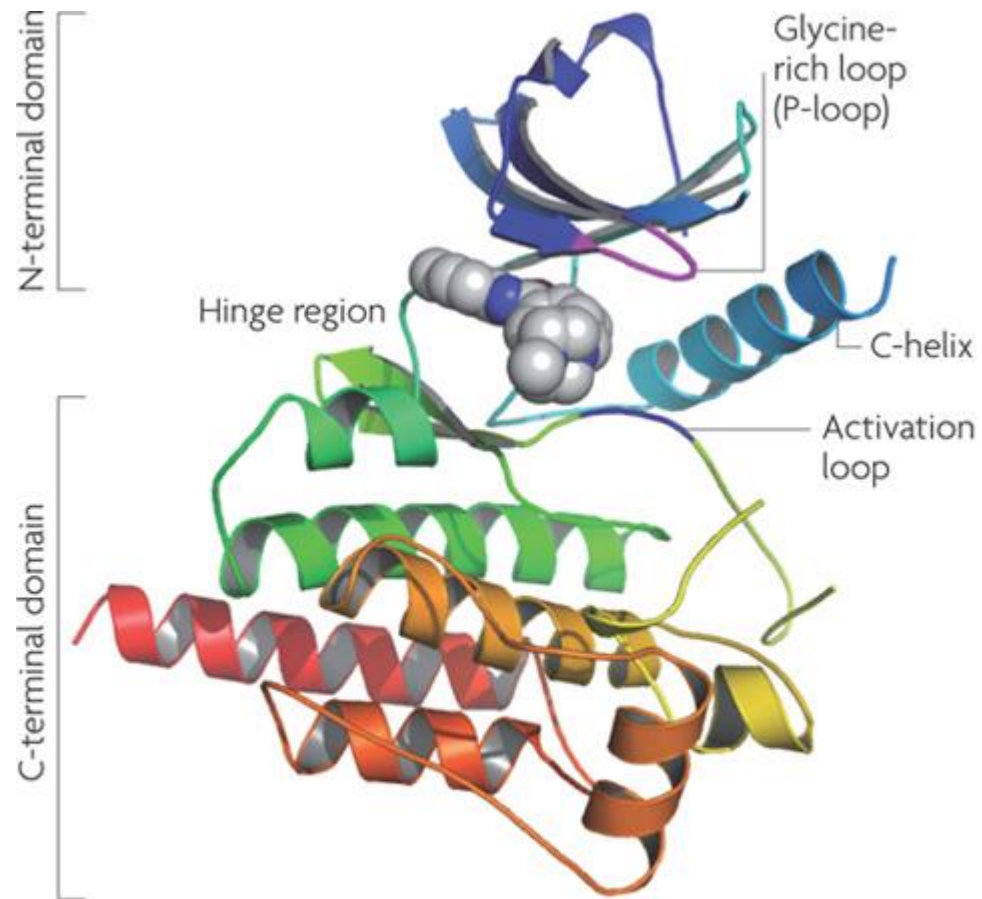
- Catalytic sites often occur at domain and subunit interfaces



Dimeric bacterial enzyme 3-isopropylmalate dehydrogenase. The active sites are indicated by the bound cofactor NADPH.



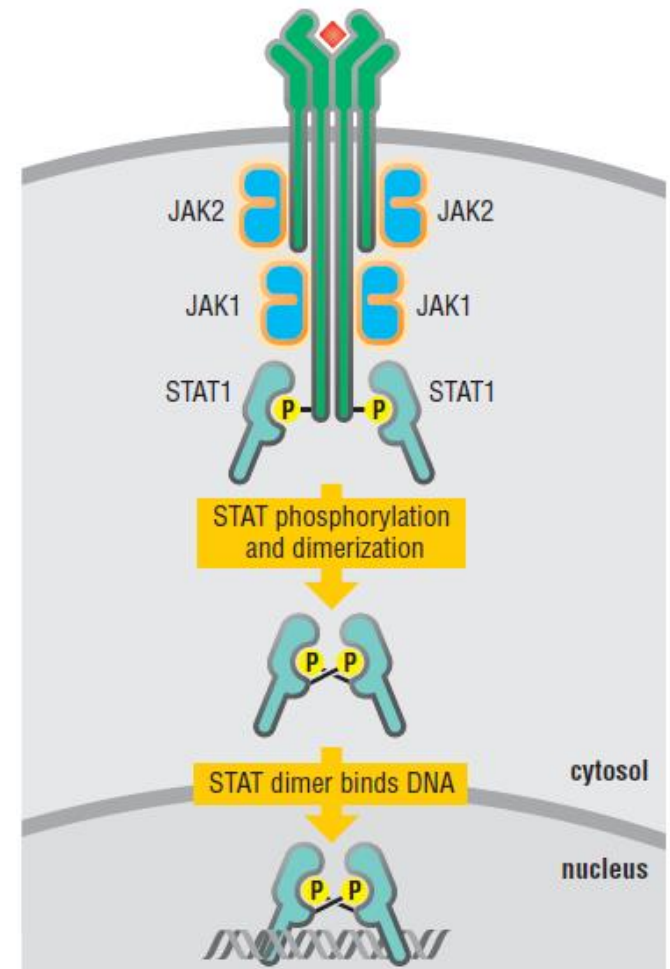
## SYK tyrosine kinase



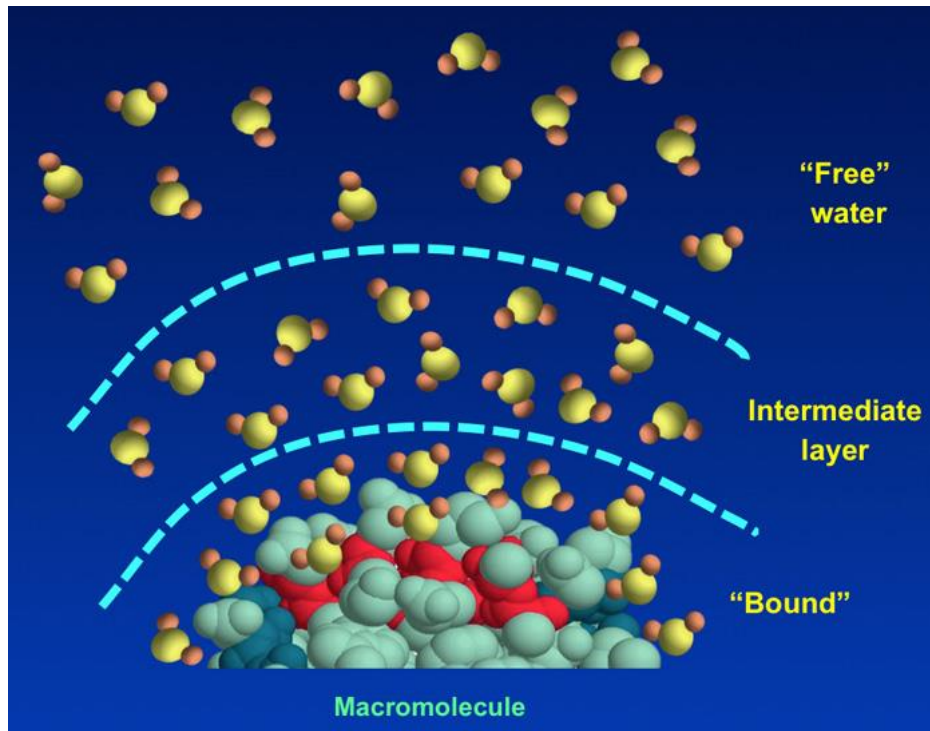
Nature Reviews | Drug Discovery

# Nature of binding sites

- Binding sites generally have a higher than average amount of **exposed hydrophobic surface**
- Binding sites for small molecules are usually **concave** and **partly hydrophobic**
- Weak interactions can lead to an **easy exchange** of partners



# Nature of binding sites

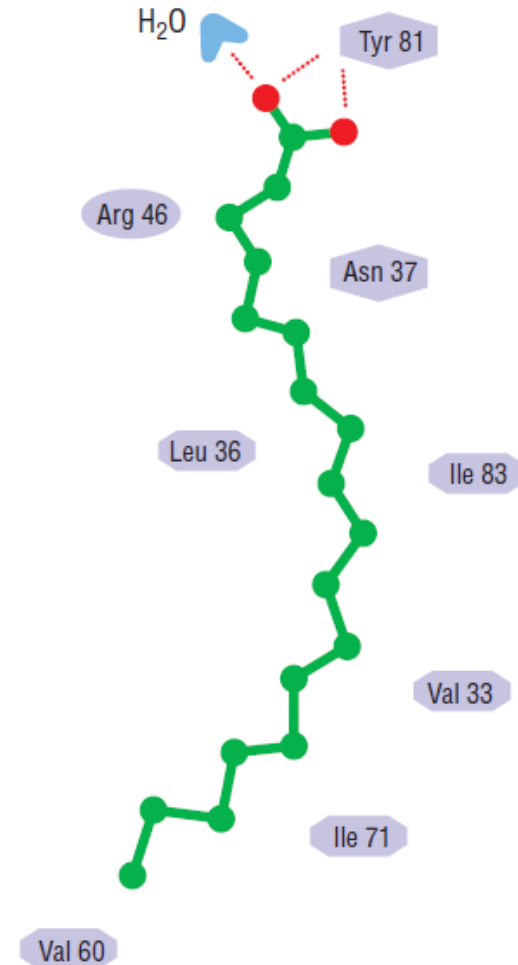


- Displacement of water drives binding events
  - The enthalpic cost of releasing the surface waters
  - Depending on the **microenvironment**
    - Polar interaction is stronger in an environment of reduced polarity than in aqueous solution



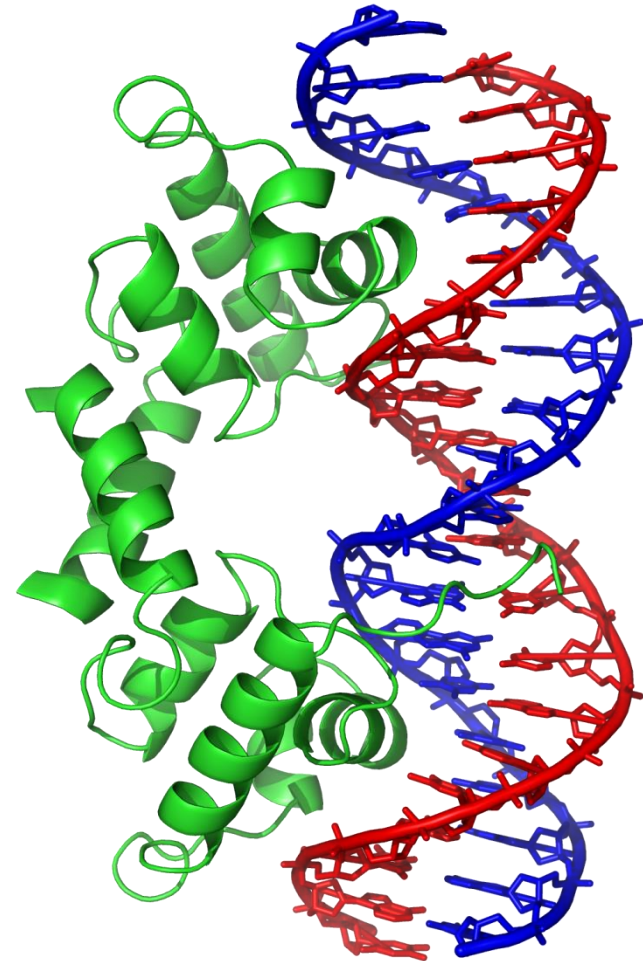
# Nature of binding sites

- High binding affinity usually means high specificity, but sometimes...
- Contributions to **binding affinity**
  - Hydrophobic interactions
- Contributions to **binding specificity**
  - **Anisotropic** or directional forces
  - Hydrogen bonding

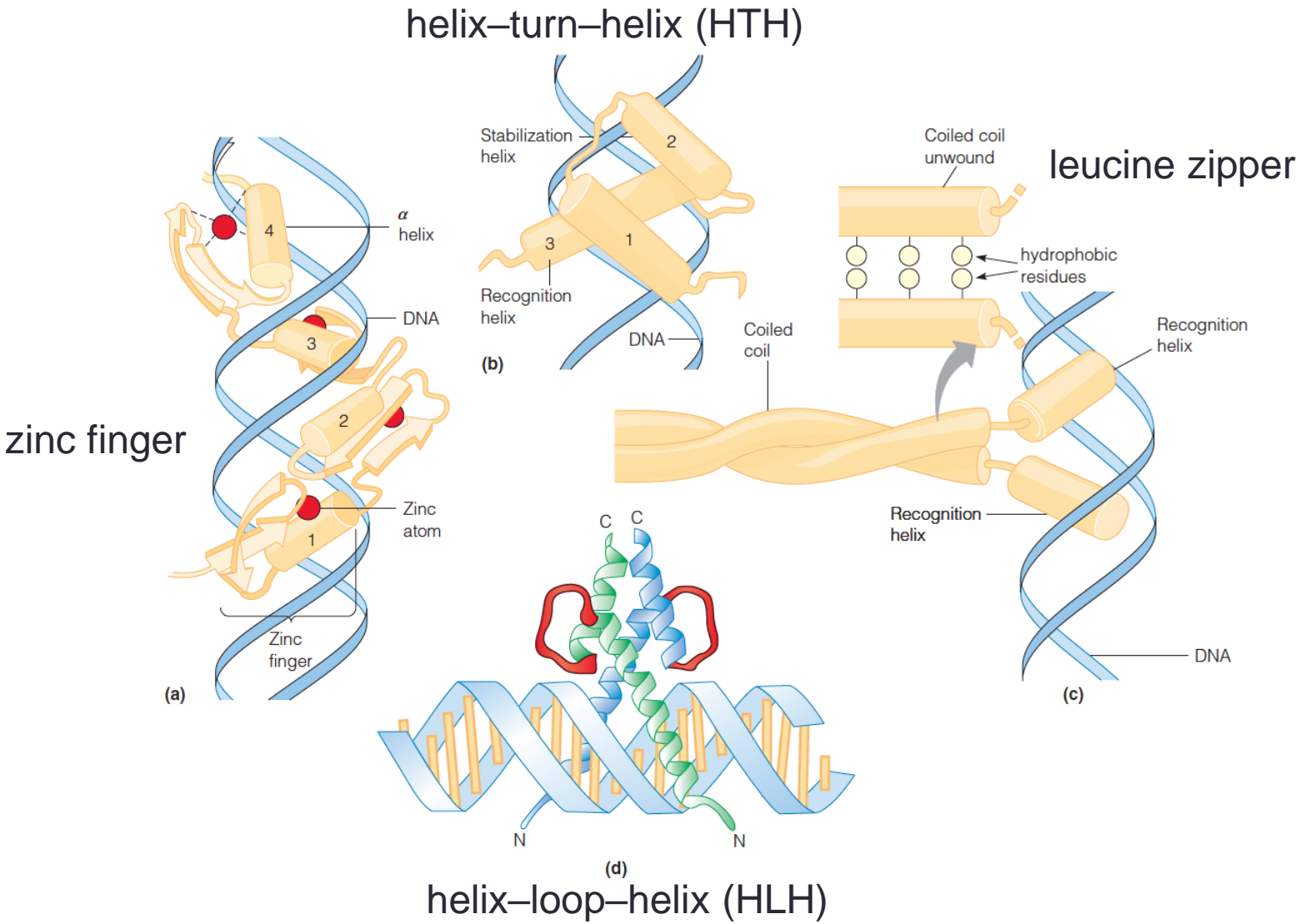


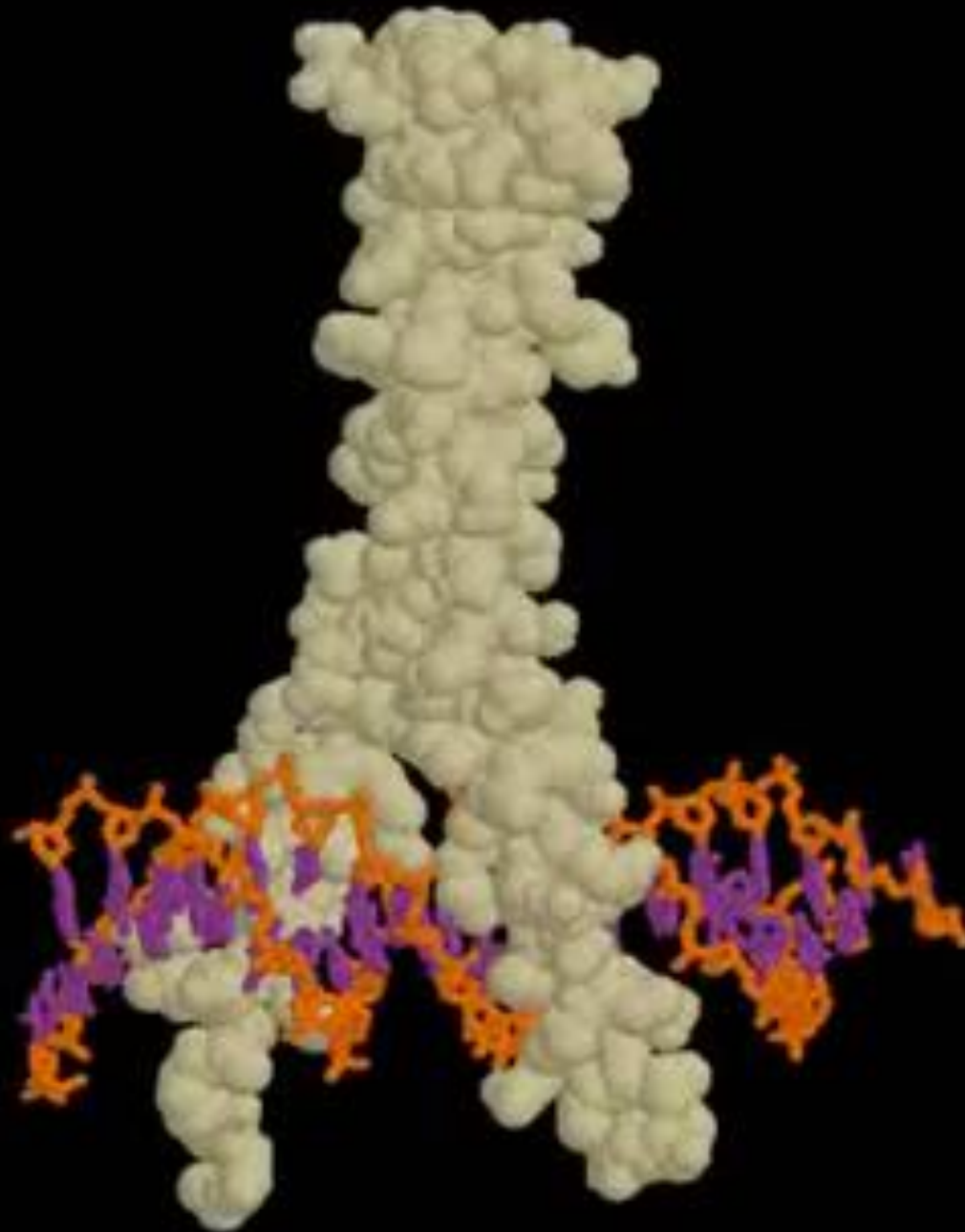
# Protein-DNA interaction

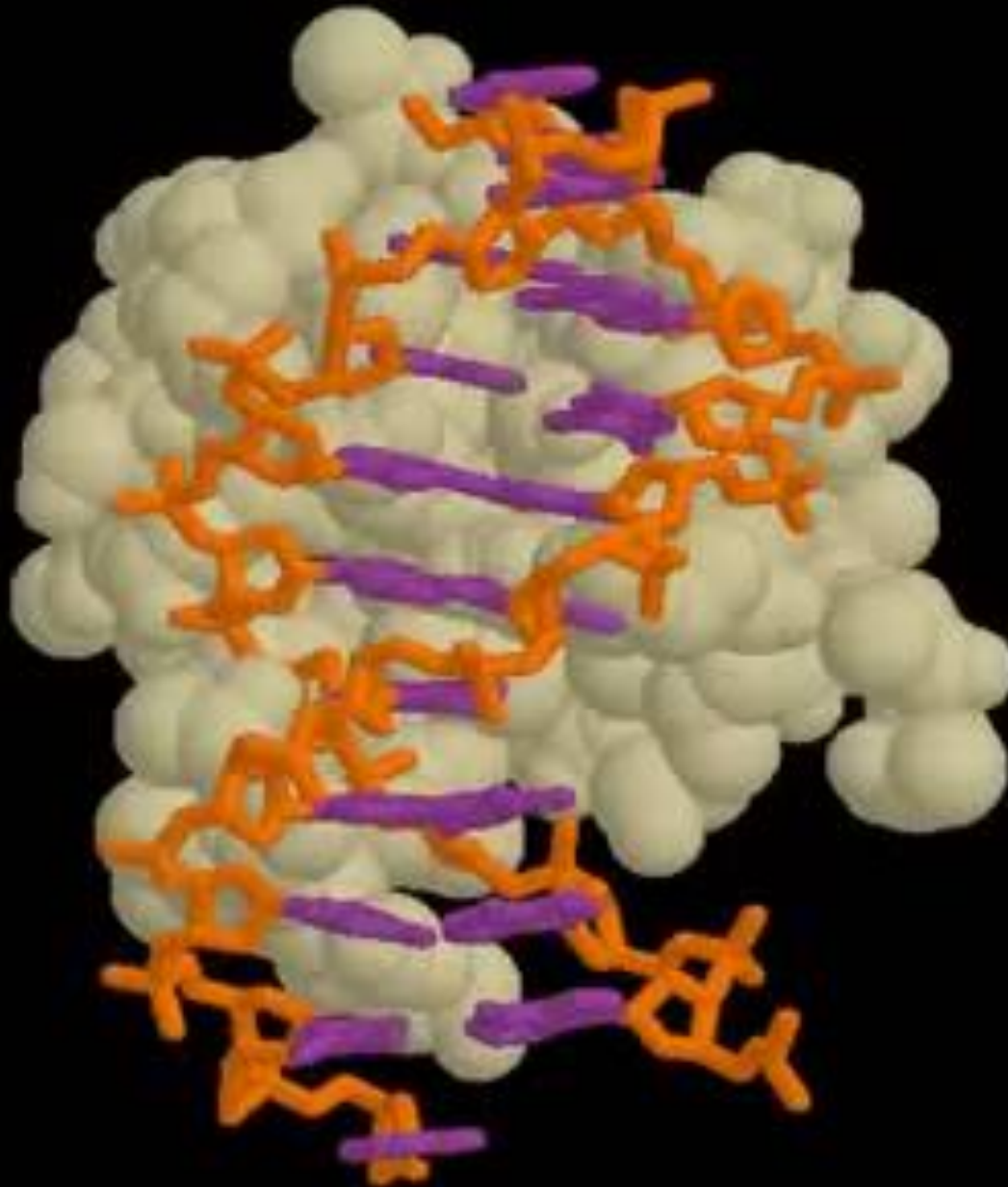
- DNA replication
- DNA modification
- DNA repair
- Transcription
- Chromosome modeling
- ...



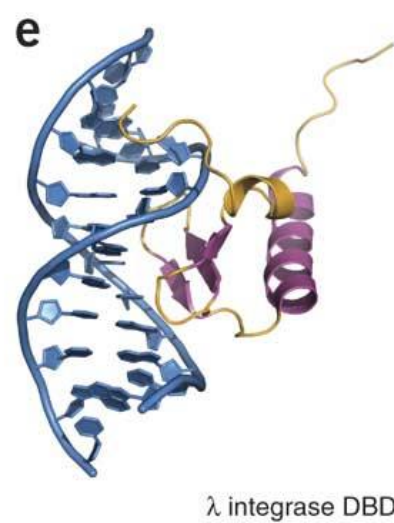
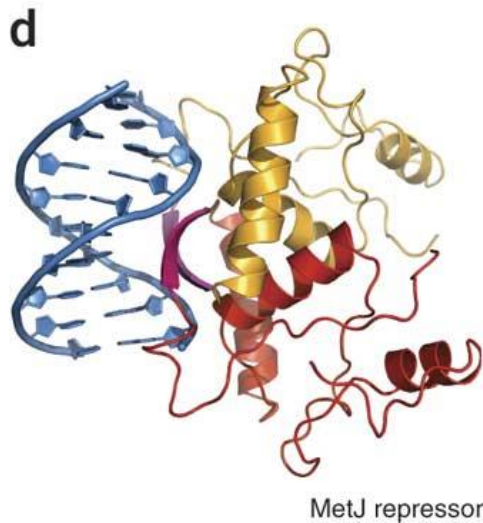
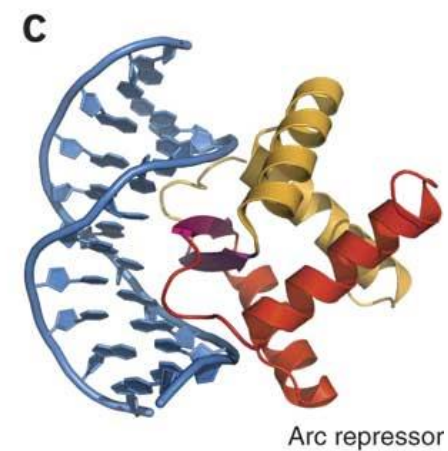
# DNA binding motifs and domains





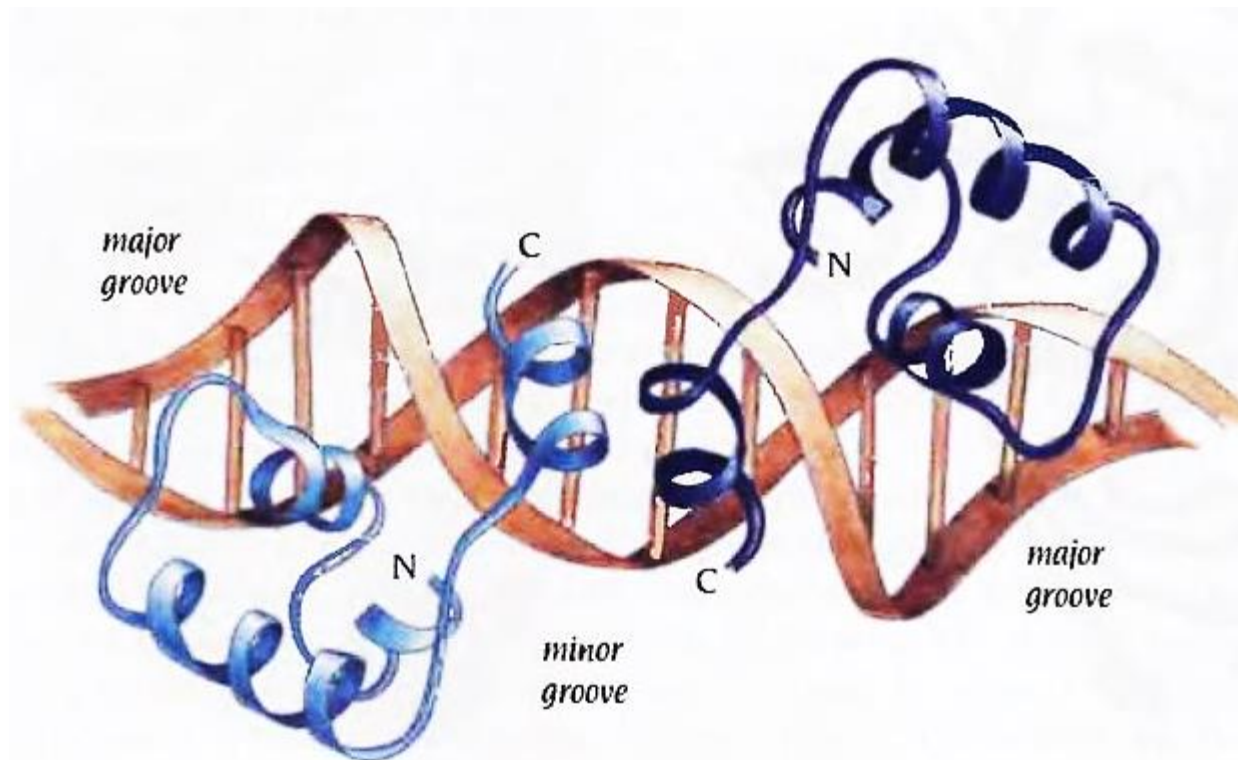


# The major grooves provide binding sites for DNA binding proteins



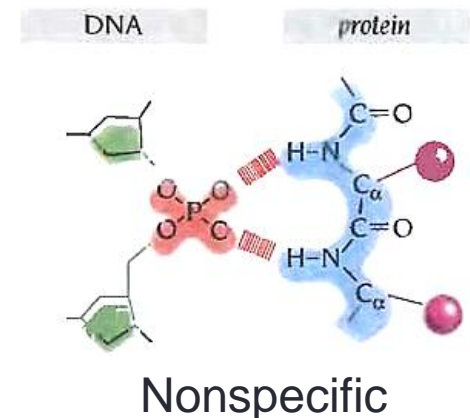
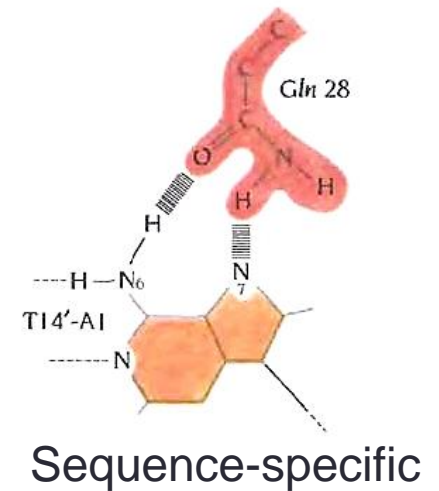
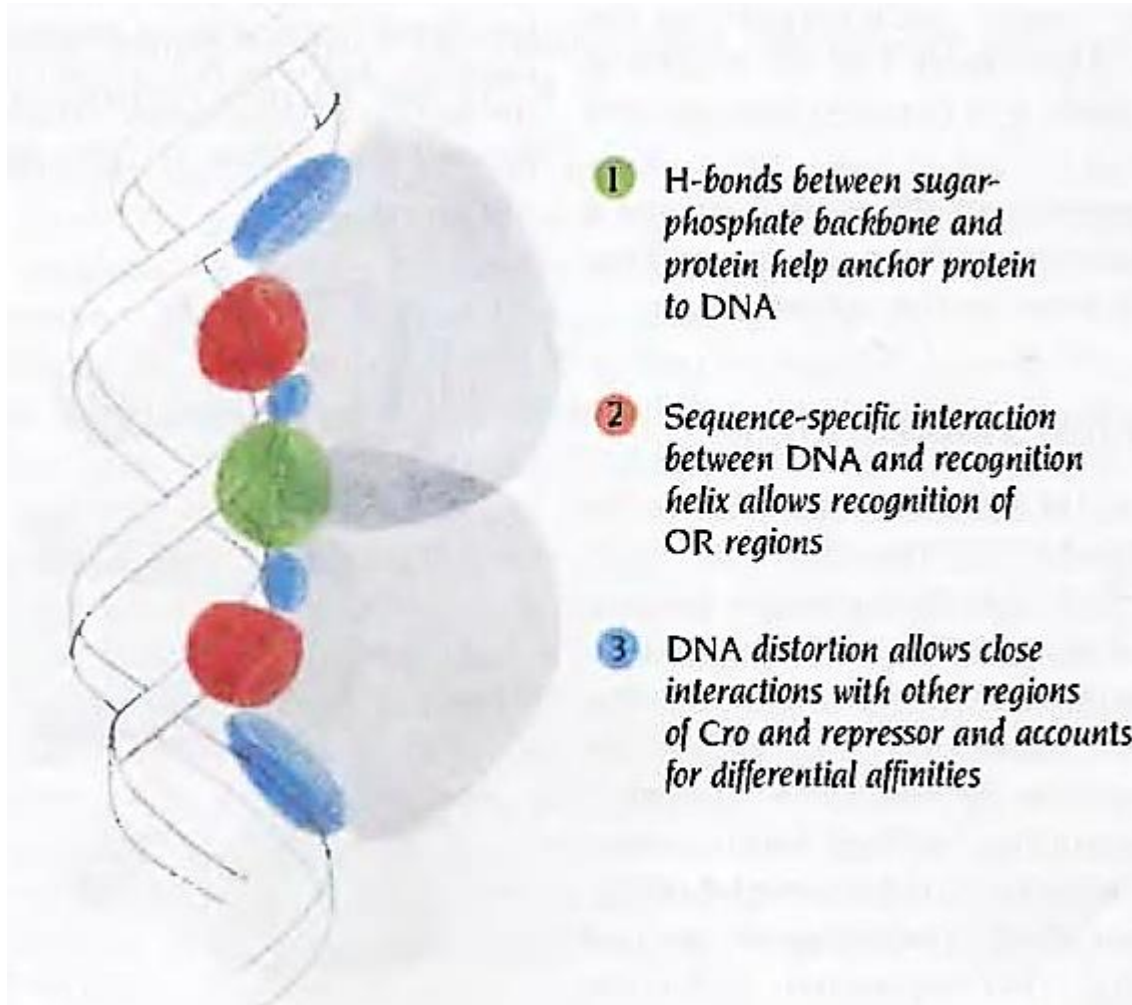


# The minor grooves may be also involved in binding



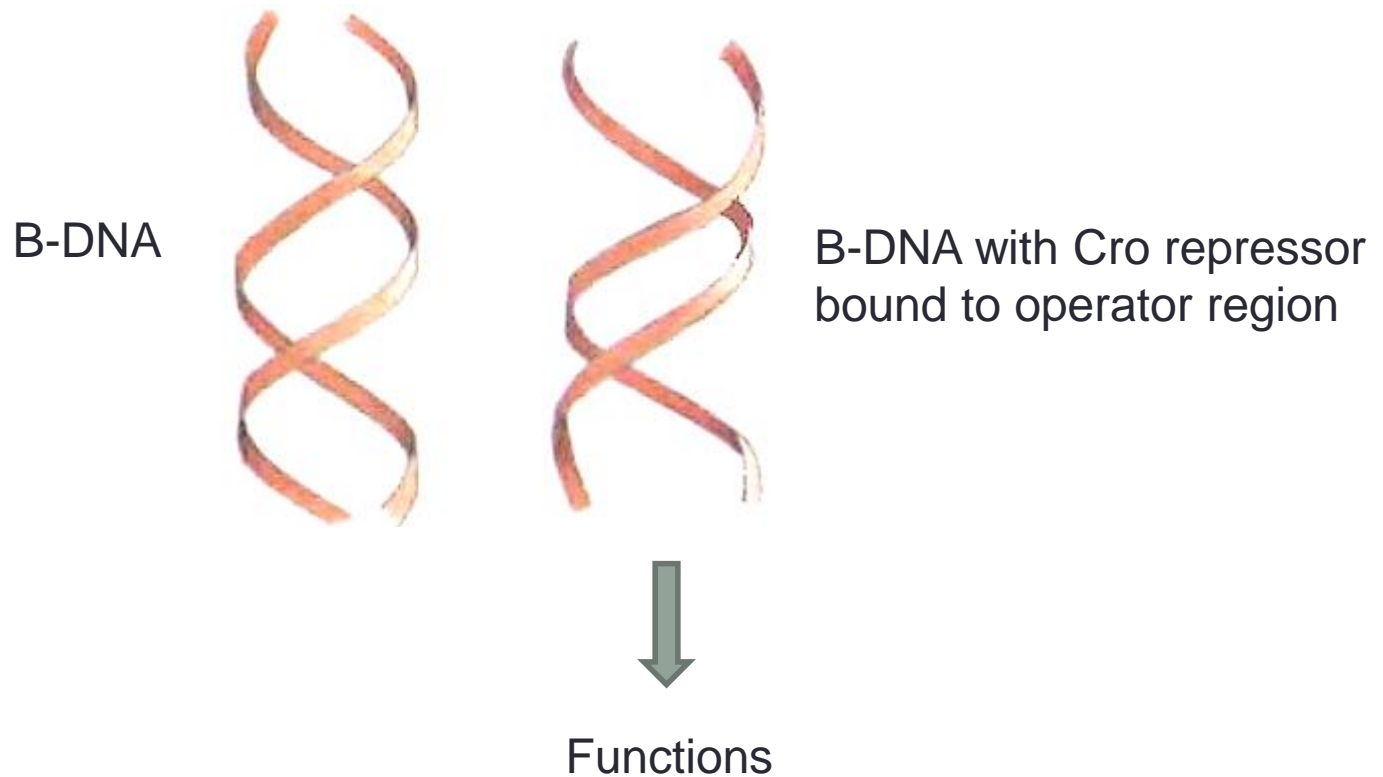
The lac repressor binds to both the major and minor grooves of DNA for distortion of the B-DNA structure

# Main features of DNA interaction with HTH motif





# Proteins impose precise distortions on DNA conformations in complexes



# Protein-RNA interaction

- Interaction with mRNA
  - Transcription
  - Translation
  - Translocation/transport
- Interaction with tRNA
  - Translation
- Interaction with rRNA
  - Translation
- RNA editing
  - Splicing
- RNA interference
- DNA editing
- ...

