

Enzymes and coenzymes II

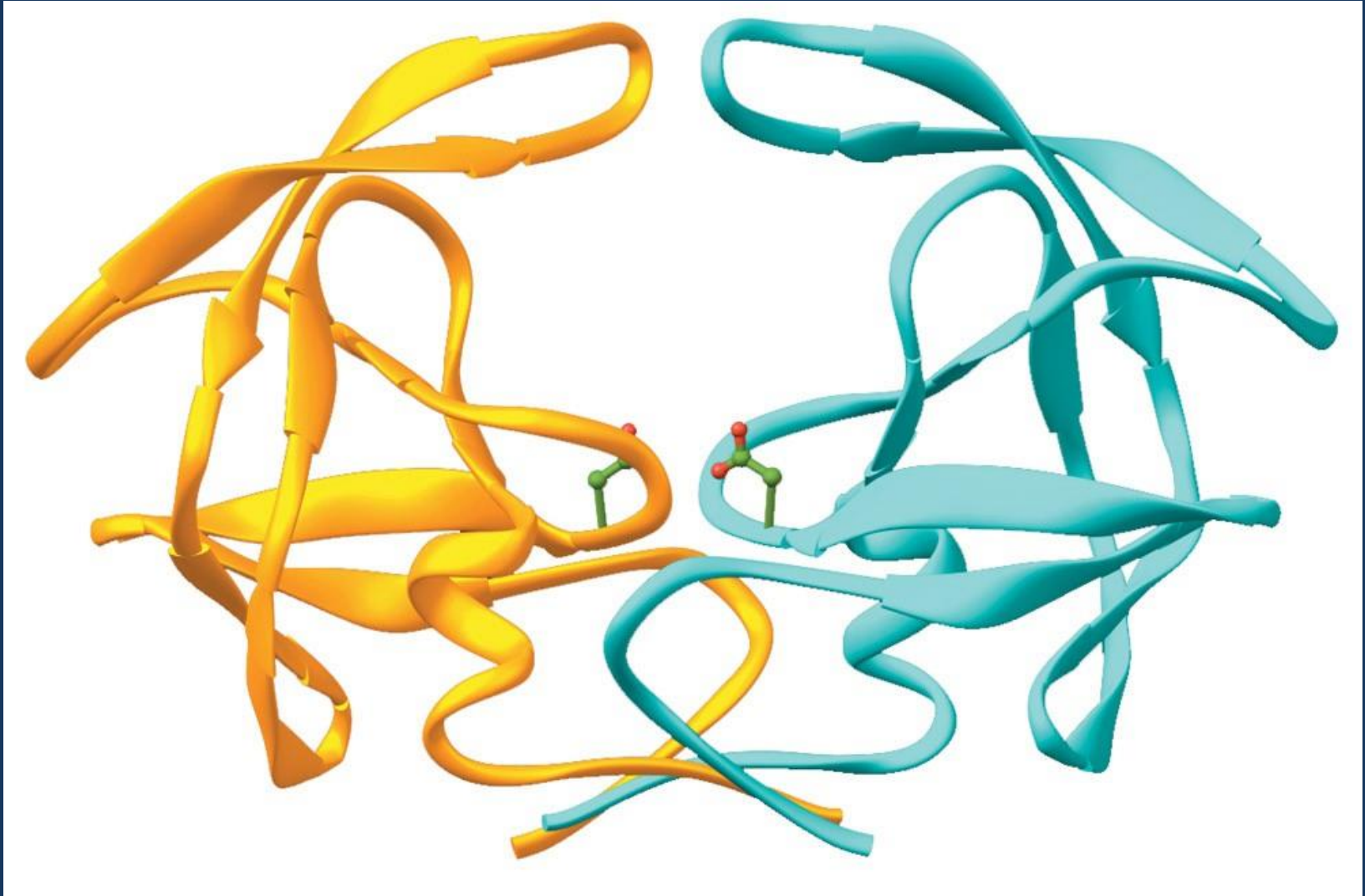
Dr. Sumbul Fatma

Clinical Chemistry Unit

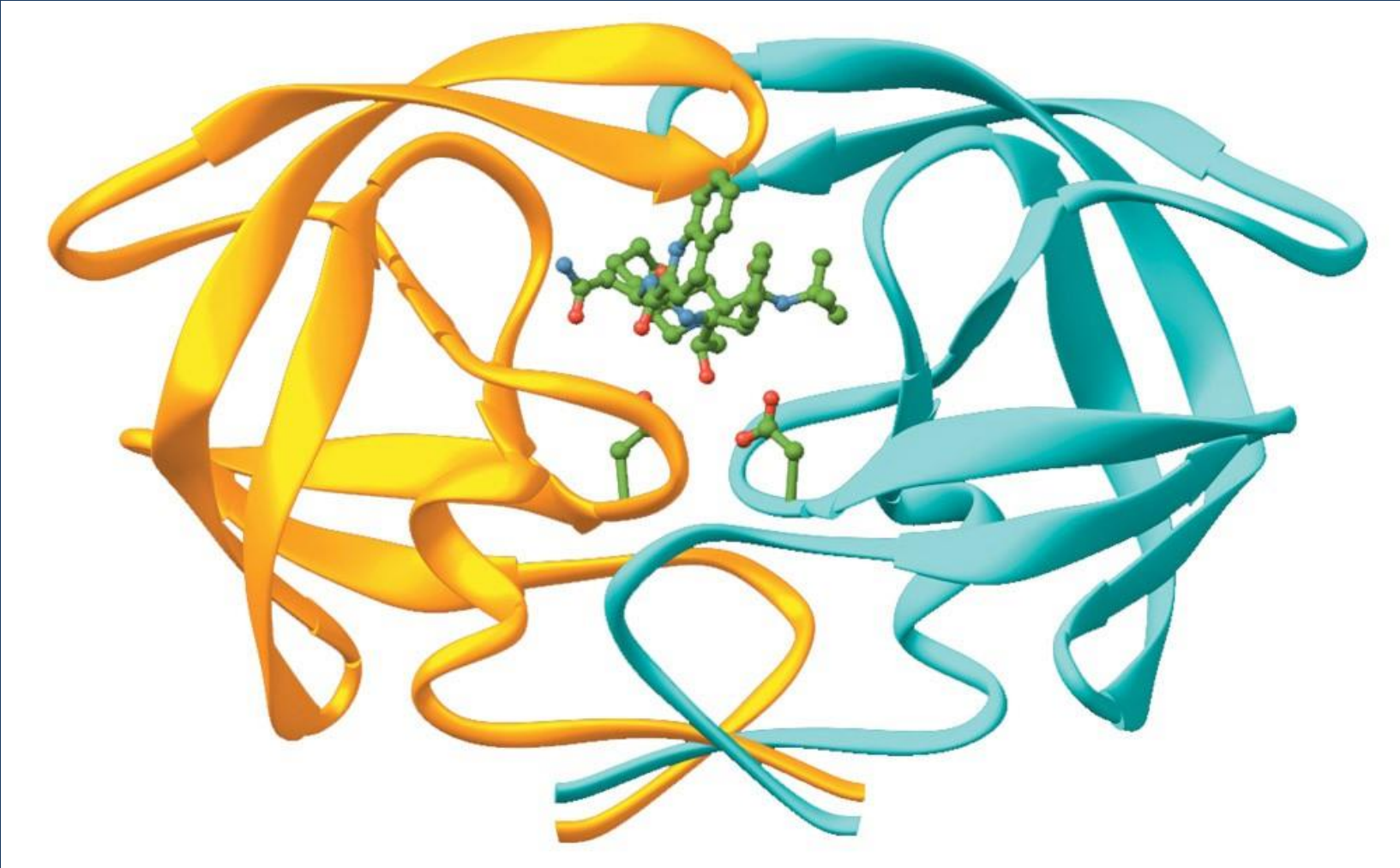
Department of Pathology

Enzyme inhibition

- Inhibition is a process in which the enzyme activity is regulated or controlled
- To inhibit means to stop the enzyme activity



An enzyme without inhibitor



An enzyme with inhibitor

Enzyme inhibition

- There are mainly two types of enzyme inhibition:
 - Competitive
 - Noncompetitive

K_i (Inhibitor constant)

- K_i is a measure of the affinity of the inhibitor for the enzyme. Also known as dissociation constant

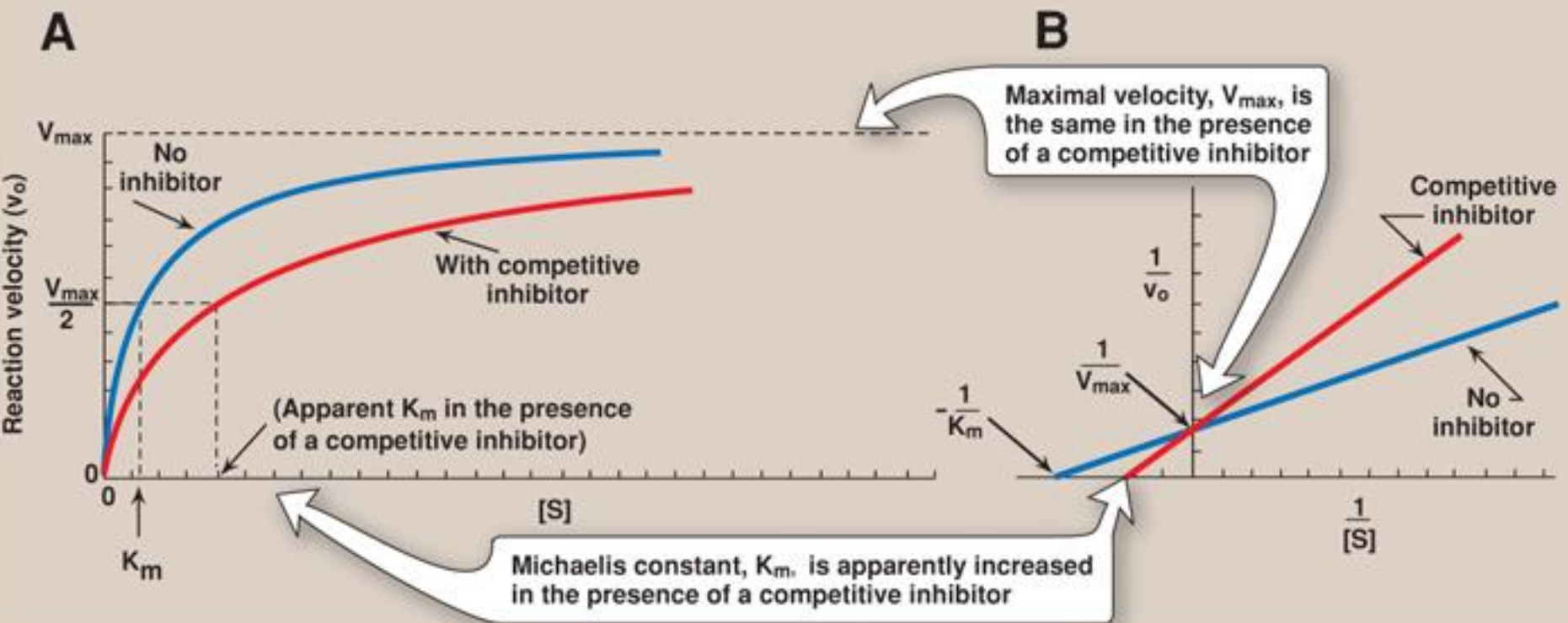
Competitive inhibition

- The inhibitor is a structural analogue that competes with the substrate for binding at the active site of enzyme
- Two equilibria are possible:



and





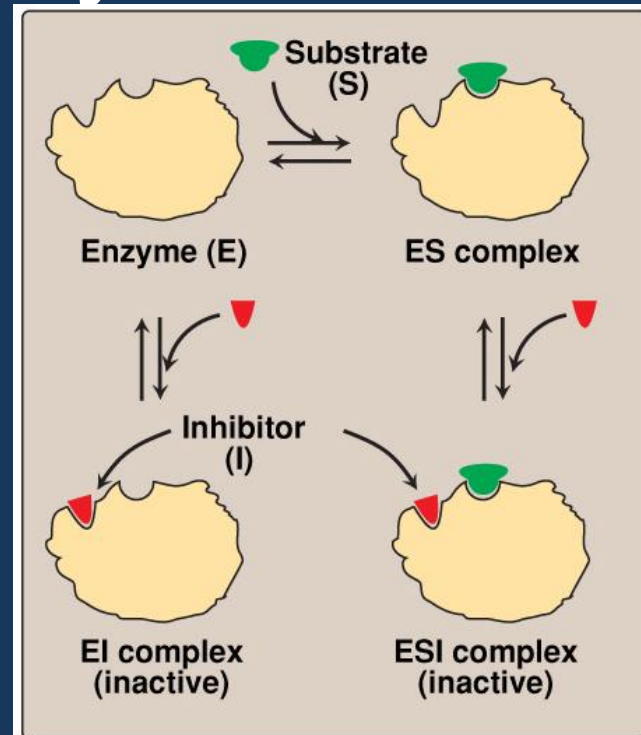
- In competitive inhibition, V_{max} is unchanged in the presence and the absence of inhibitor
- The value of K_m is increased because substrate and inhibitor compete for binding at the same site
- A higher concentration of substrate is required to achieve half-maximal velocity

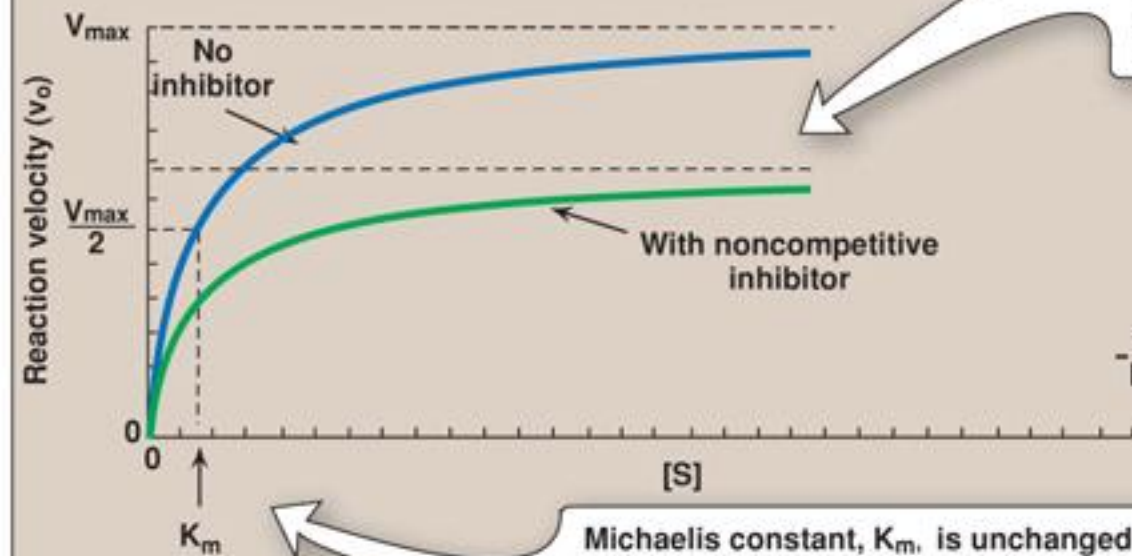
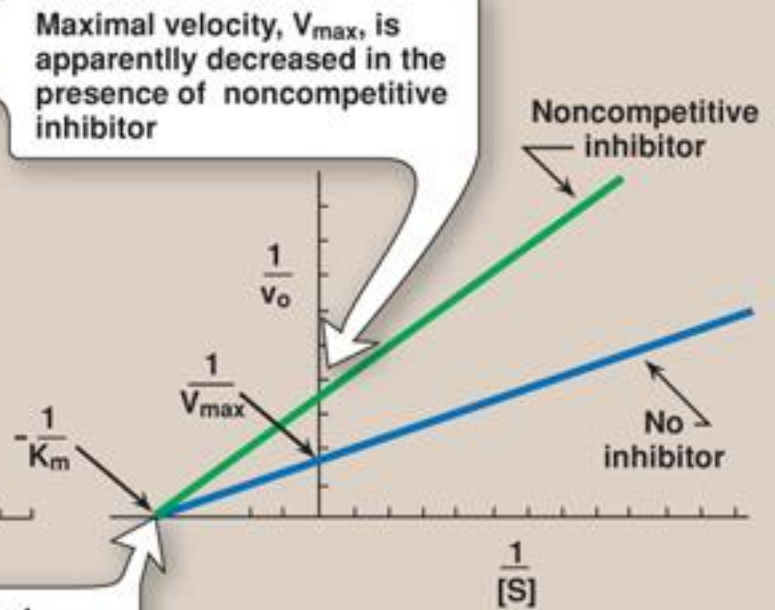
Noncompetitive inhibition

- The inhibitor does not have structural similarity to the substrate
- The inhibitor binds to the enzyme at a site away from the substrate binding site
- No competition exists between the inhibitor and the substrate
- The inhibitor can bind to a free enzyme or to an enzyme-substrate complex
- In both cases the complex is catalytically inactive



- The value of V_{\max} is decreased by the inhibitor, but K_m is unchanged because the affinity of S for E is unchanged



A**B**

Michaelis constant, K_m , is unchanged in the presence of a noncompetitive inhibitor

Regulation of enzyme activity

- Regulatory enzymes usually catalyze the first or an early reaction in a metabolic pathway
- They catalyze a rate limiting reaction that controls the overall pathway
- They may also catalyze a reaction unique to that pathway known as committed step

- **Feedback inhibition:**

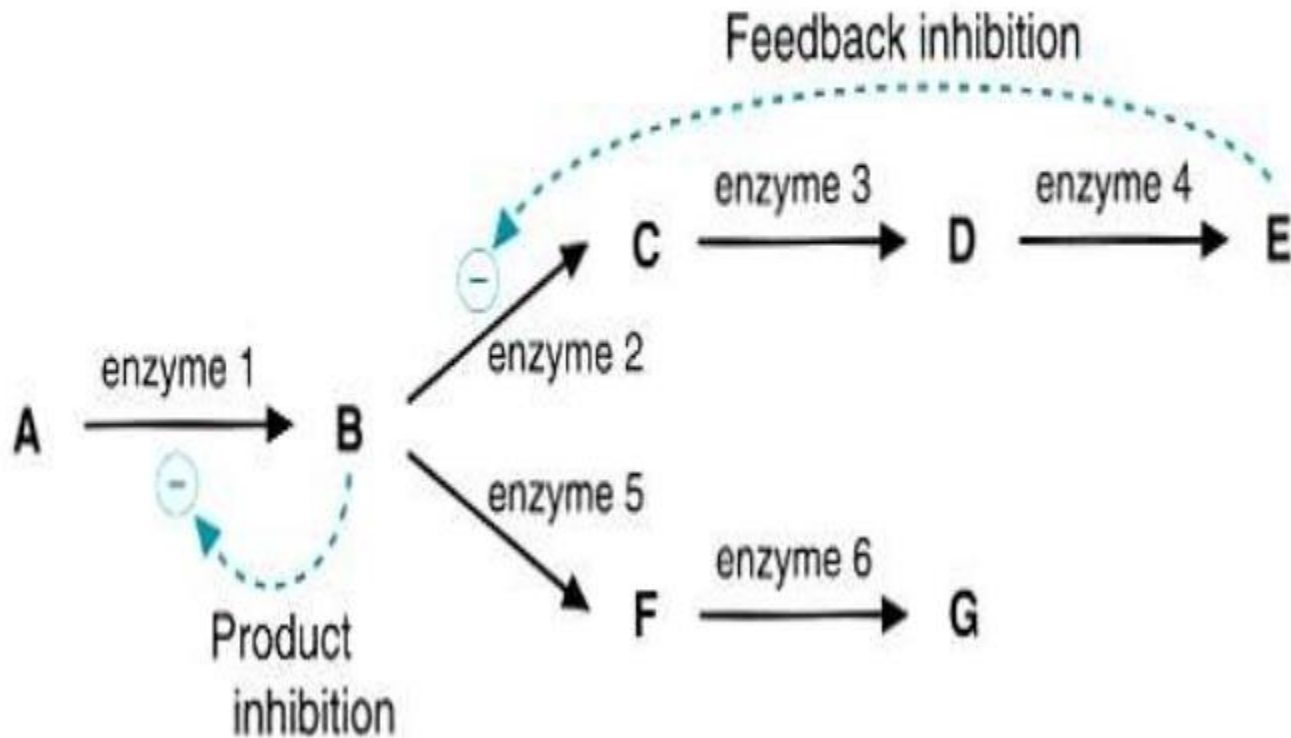
- When the end product of a metabolic pathway exceeds its concentration limit, it inhibits the regulatory enzyme to normalize the pathway (feedback inhibition)

- **Feed positive activation:**

- When the end product of a metabolic pathway is below its concentration limit, it activates the regulatory enzyme to normalize the pathway



Feedback Inhibition



Types of regulation

- **Allosteric enzyme regulation**
 - The enzymes in metabolic pathways whose activities can be regulated by certain compounds that bind to enzyme other than the catalytic site are known as allosteric enzymes
 - The term “allosteric” came from Greek word “allos” meaning “other”

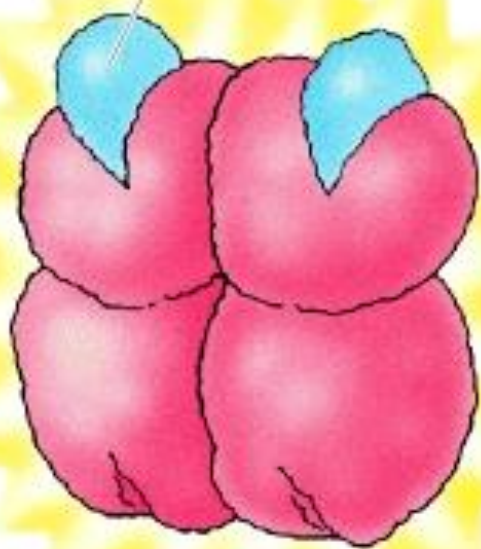
- **Cooperative binding**

- The process by which binding of a ligand to a regulatory site affects binding of the same or of another ligand to the enzyme is known as cooperative binding

- **Binding of an allosteric modulator causes a change in the conformation of the enzyme**
- **This causes a change in the binding affinity of enzyme for the substrate**

Active

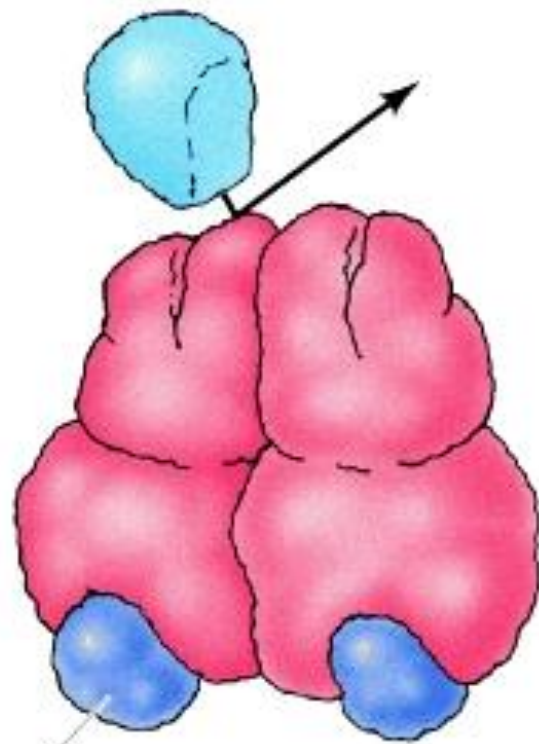
Substrate bound
to active site



Inactive



Inhibitor bound
to allosteric site



- The effect of a modulator may be positive (activation) or negative (inhibition)
 - Positive: increased E, S affinity
 - Negative decreased E, S affinity
- Most allosteric enzymes are oligomers (two or more polypeptide chains or subunits)
- The subunits are known as protomers

- **Two types of interactions occur in allosteric enzymes:**
 - **Homotropic**
 - **Heterotropic**
- **Homotropic: Effect of one ligand on the binding of the same ligand (a regulatory enzyme modulated by its own substrate)**
- **Heterotropic: Effect of one ligand on the binding of a different ligand**

Enzymatic diagnosis and prognosis of diseases

- Enzymes are used clinically in three ways:
 - As indicators of enzyme activity or conc. in body fluids (serum, urine) in the diagnosis/prognosis of diseases
 - As analytical reagents in measuring activity of other enzymes or compounds in body fluids
 - As therapeutic agents

- The most commonly used body fluids for measuring enzyme activity are **serum** and **plasma**
- **There are:**
 - **Plasma-specific enzymes**
 - **Nonplasma-specific enzymes**

Serum markers in the diagnosis of diseases

- Heart disease
- Pancreatic diseases
- Liver diseases

Reference

- **Lippincott- Illustrated Reviews in Biochemistry, 4th Edition**