C1.1 Enzymes and metabolism

Interaction and interdependence—Molecules

Standard level and higher level: 3 hours

Additional higher level: 2 hours

Guiding questions

• In what ways do enzymes interact with other molecules?

• What are the interdependent components of metabolism?

Recommended prior learning: B1.2 Proteins

SL and HL

C1.1.1—Enzymes as catalysts
Students should understand the benefit of increasing rates of reaction in cells.
Catalysts are substances that increase the rate of a chemical reaction without being used up in the reaction itself. **Enzymes** are a type of catalyst (proteins made by living organisms) used by cells due to: • Faster **energy production** to support muscles during exercise and other energy-heavy activities • Faster **waste removal** to prevent their accumulation and toxicity • Faster **response to injury**, such as the blood clotting cascade • Faster **homeostatic responses** to maintain internal conditions like temperature and pH • Faster **cellular communication** during signaling pathways and transduction • Faster **cellular regeneration and repair** of tissues

C1.1.2—Role of enzymes in metabolism
Students should understand that metabolism is the complex network of interdependent and interacting chemical reactions occurring in living organisms. Because of enzyme specificity, many different enzymes are required by living organisms, and control over metabolism can be exerted through these enzymes.
Metabolism is a term that describes all *enzyme-catalyzed chemical reactions* that sustain the life of a living organism. Because of enzyme specificity, many different enzymes are required by living organisms, and control over metabolism can be exerted through these enzymes.

C1.1.3—Anabolic and catabolic reactions
Examples of anabolism should include the formation of macromolecules from monomers by condensation reactions including protein synthesis, glycogen formation and photosynthesis. Examples of catabolism should include hydrolysis of macromolecules into monomers in digestion and oxidation of substrates in respiration.
There are two types of metabolism: **Anabolism** describes the enzyme-catalyzed chemical reactions that synthesize **macromolecules** (big, complex ones) from **monomers** (small, simple molecules). Examples include photosynthesis, protein synthesis, and glycogen formation. **Catabolism** describes the enzyme-catalyzed chemical reactions that break down macromolecules into monomers (a cat like to breaks stuff, like catabolism). Examples include digestion and cellular respiration. Organic molecules are synthesized by condensation reactions (removing a water molecule from the monomers to join them, i.e. forming a peptide bond) and broken down by hydrolysis reactions (using water, *hydro*, to break the molecule down, *lysis*).

C1.1.4—Enzymes as globular proteins with an active site for catalysis

Include that the active site is composed of a few amino acids only, but interactions between amino acids within the overall three-dimensional structure of the enzyme ensure that the active site has the necessary properties for catalysis.

Enzymes are globular proteins composed of peptide chains. Of the many amino acids within its structure, a special few are involved in catalyzing chemical reactions. The region in which these special, few amino acids exist is called the **active site** of the enzyme, as it is the *site* that carries out the enzyme's *activity*.

Despite this, molecular interactions between *all* of the amino acids within the enzyme determine whether the active site is actually 'active' and able to catalyze the chemical reaction.

C1.1.10—Effect of enzymes on activation energy

Application of skills: Students should appreciate that energy is required to break bonds within the substrate and that there is an energy yield when bonds are made to form the products of an enzyme-catalyzed reaction. Students should be able to interpret graphs showing this effect.

Enzymes increase the rate of a chemical reaction by decreasing its **activation energy**, which is the minimum energy required for the reaction to take place. They do this by providing an alternative mechanism/pathway for the reaction that requires less activation energy than the one that would have occurred without an enzyme.

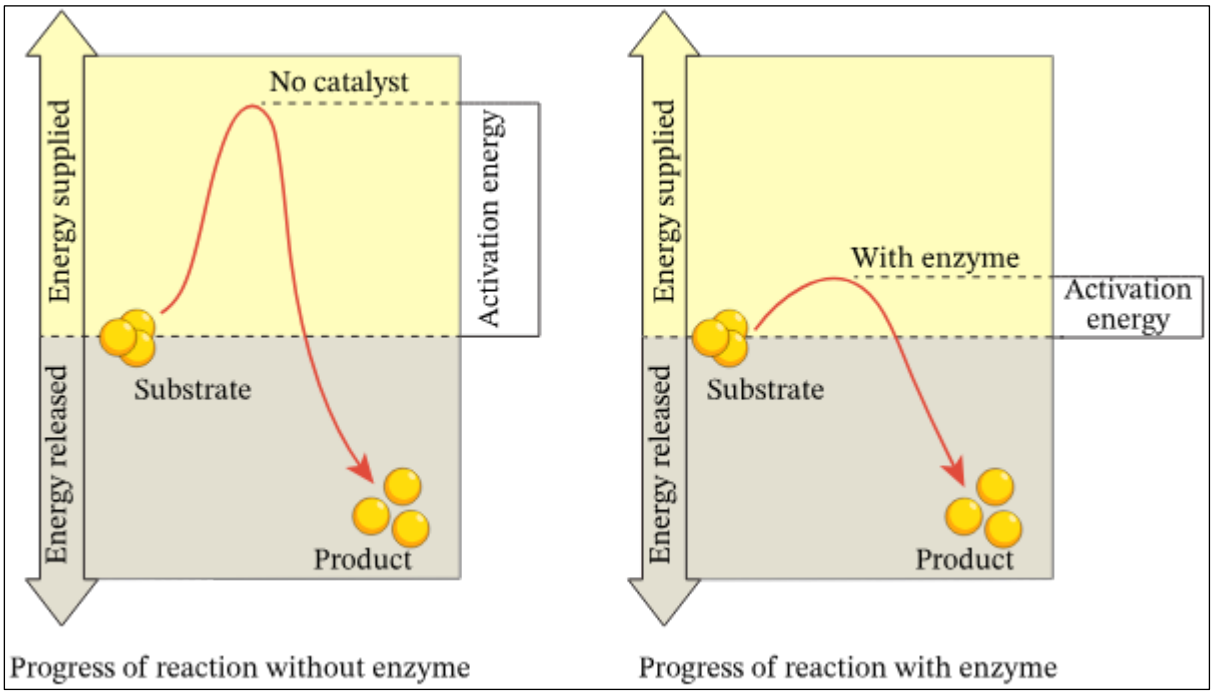


Figure 1: energy-profile diagram with and without a catalyst/enzyme (Nagwa).

C1.1.5—Interactions between substrate and active site to allow induced-fit binding

Students should recognize that both substrate and enzymes change shape when binding occurs.

The **induced-fit theory** is a model postulating that the **substrate**, the chemical substance that binds to the enzyme's active site, does more than simply fit perfectly into the active site – it causes a change in the enzyme's shape so as to properly align the special few amino acids (called catalytic groups) on its surface. The substrate also changes its shape when binding occurs to further optimize the fitting.

Analogy: when you put on a glove, your hand induces slight changes to the glove's shape so as to perfectly fit it, even though the glove already is shaped like a hand. Similarly, although an enzyme's active site is already a very good match for the substrate, the binding of the substrate to it induces slight conformational changes so as to ensure optimal fitting.

C1.1.6—Role of molecular motion and substrate-active site collisions in enzyme catalysis

Movement is needed for a substrate molecule and an active site to come together. Sometimes large substrate molecules are immobilized while sometimes enzymes can be immobilized by being embedded in membranes.

Brownian motion is a phenomenon in which a chemical substance is naturally in a constant state of random movement, colliding with other molecules as they move. This movement is how a substrate and enzyme come together; if they collide at the **correct orientation** (i.e. the substrate must collide with the active site of the enzyme body at the correct angle) with **sufficient energy** (enough to bypass the activation energy), the catalyzed reaction will take place.

Enzymes and substrates can either be present within the cell's cytoplasm, embedded within the plasma membrane, or fixed onto a solid surface (i.e. algae balls) – if they are fixed in a particular place, they are **immobilized**, which incurs several benefits:

- Greater resistance to temperature and pH fluctuations
- Reduced costs when separating enzyme from substrate in industrial production
- Greater reusability as immobilized enzymes last longer
- Ability to perform localized reactions in specific parts of the cell or organelle

C1.1.7—Relationships between the structure of the active site, enzyme–substrate specificity and denaturation

Students should be able to explain these relationships.

The chemical structure of the enzyme's active site determine its shape and thus the substrate that can bind to the enzyme, leading to **enzyme-substrate specificity**. Some enzymes are so specific they can only fit one specific substrate, while others can bind to an entire (but specific) group of substrates.

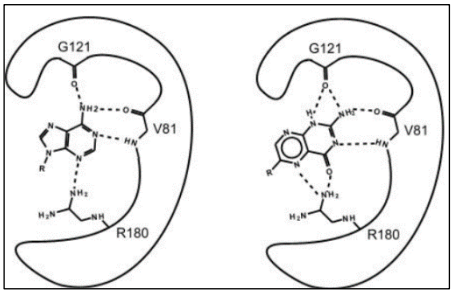


Figure 2: the same enzyme bound to two different but similar substrates- notice how the amino acids on the active site (G121, V81, R180) form hydrogen bonds with the substrates. "The unique combination of amino acids, their positions, sequences, structures, and properties, creates a very specific chemical environment within the active site" that only specific substrate(s) can fit into (Libretexts).

C1.1.8—Effects of temperature, pH and substrate concentration on the rate of enzyme activity

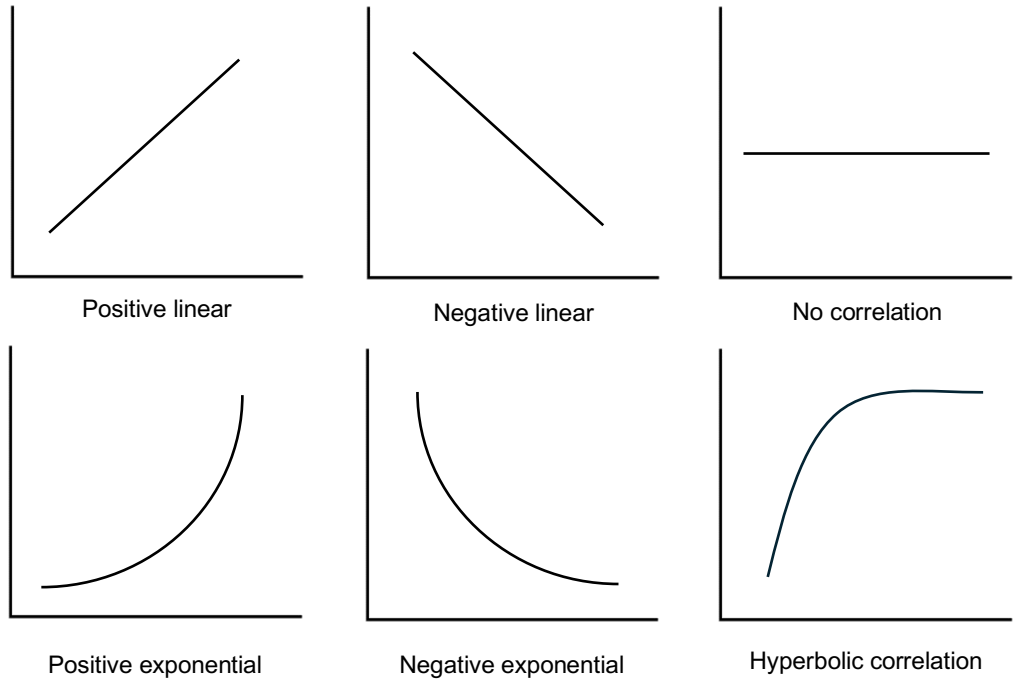
The effects should be explained with reference to collision theory and denaturation.
Application of skills: Students should be able to interpret graphs showing the effects.

Temperature: increasing the temperature increases the probability of successful collisions between the enzyme and substrate, leading to greater enzyme activity. Once the optimum temperature is surpassed, the enzyme begins to irreversibly denature, decreasing the concentration of functioning enzymes thus lowering enzyme activity.

pH: H^+ concentration interferes with the interactions between amino acids within the enzyme's structure. Any deviation away from the optimum pH (in which H^+ concentration enables amino acid interactions that optimize the shape of the active site), whether an increase or decrease, will denature and decrease enzyme activity.

Substrate concentration: increasing substrate concentration increases the probability of successful collisions between the enzyme and substrate, leading to greater enzyme activity. As the active sites of the enzymes become saturated, the rate of reaction starts to gradually level off and eventually plateau when all active sites are occupied.

NOS: Students should be able to describe the relationship between variables as shown in graphs. They should recognize that generalized sketches of relationships are examples of models in biology. Models in the form of sketch graphs can be evaluated using results from enzyme experiments.



The above graphs are general sketches of relationships that are examples of mathematical models in biology. A model of enzyme-catalyzed reactions is hyperbolic, while a model of bacterial population growth is exponential, and so on. Quantifying observations of biological phenomena into such models allows us to predict trends and better understand experimental results.

C1.1.9—Measurements in enzyme-catalyzed reactions

Application of skills: Students should determine reaction rates through experimentation and using secondary data.

Measured quantity	Units	Apparatus / method
Volume of gas	cm^3	Gas syringe / U-Tube
Concentration of gas	$moldm^{-3}$	Gas probe
Temperature	°C	Thermometer / Temperature probe
Acidity	pH	pH meter / Acid indicator
Absorbance of light	Au or %	Spectrophotometer / Colorimeter

Additional higher level

C1.1.11—Intracellular and extracellular enzyme-catalyzed reactions

Include glycolysis and the Krebs cycle as intracellular examples and chemical digestion in the gut as an extracellular example.

1. **Glycolysis** is the breakdown of glucose into two pyruvate molecules in the cytoplasm, which involves phosphorylation of the glucose molecule. This step is catalyzed by the enzyme **hexokinase**.
2. **Fumarase** catalyzes the conversion of fumarate to L-malate in the mitochondria in the Krebs Cycle.
3. **Amylase**, **lipase**, and **proteases** catalyze the extracellular digestion of food in humans.

C1.1.12—Generation of heat energy by the reactions of metabolism

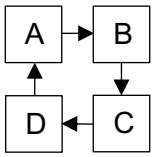
Include the idea that heat generation is inevitable because metabolic reactions are not 100% efficient in energy transfer. Mammals, birds and some other animals depend on this heat production for maintenance of constant body temperature.

Chemical reactions are never 100% efficient, so some energy is lost as heat. Mammals, birds and some other animals depend on this heat production for maintenance of constant body temperature, i.e. when humans are cold, they shiver as the energy produced from muscle movement heats the body up.

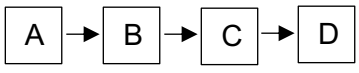
C1.1.13—Cyclical and linear pathways in metabolism

Use glycolysis, the Krebs cycle and the Calvin cycle as examples.

Cyclic metabolic pathways involve reactions in which the product of one step is a reactant in another.



Linear metabolic pathways involve reactions in which the reactant is transformed through a series of steps into a final product.



C1.1.14—Allosteric sites and non-competitive inhibition

Students should appreciate that only specific substances can bind to an allosteric site. Binding causes interactions within an enzyme that lead to conformational changes, which alter the active site enough to prevent catalysis. Binding is reversible.

Enzymes can be regulated in ways that either promote or reduce their activity in order to cater for the metabolic needs of the cell.

Competitive inhibition: occurs when an inhibitor molecule is structurally similar to the substrate and is able to bind (and compete against the substrate) to the active site of the enzyme, effectively blocking the substrate from binding to the enzyme thus leading to a lower reaction rate.

Noncompetitive inhibition: occurs when an inhibitor molecule is not structurally similar to the substrate and binds reversibly to the allosteric site of the enzyme, causing chemical interactions with the enzyme that lead to conformational changes, which alters the active site an enough of an extent to prevent catalysis.

An **allosteric site** is a distinct region within the enzyme's structure where **regulatory molecules**, like noncompetitive inhibitors, can bind to the enzyme and change the active site's conformation so as to increase or decrease the enzyme's affinity to its substrate. **Enzyme affinity** is a measure of how readily an enzyme binds to its substrate; the higher the affinity the more optimal the active site's conformation is for the substrate.

When noncompetitive inhibitors bind to the allosteric site, they decrease the enzyme's affinity as they induce a conformational change in the active site that makes its shape less optimal for fitting the substrate.

C1.1.15—Competitive inhibition as a consequence of an inhibitor binding reversibly to an active site

Use statins as an example of competitive inhibitors. Include the difference between competitive and noncompetitive inhibition in the interactions between substrate and inhibitor and therefore in the effect of substrate concentration.

Statins competitively inhibit **HMG-CoA** (3-hydroxy-3-methylglutaryl-coenzyme A), the enzyme catalyzing the rate-determining (major) step in cholesterol synthesis, which is useful in patients with high cholesterol levels.

The **maximum** rate of reaction with an enzyme can be restored during competitive inhibition by simply increasing the concentration of the substrate, but **not** in noncompetitive inhibition.

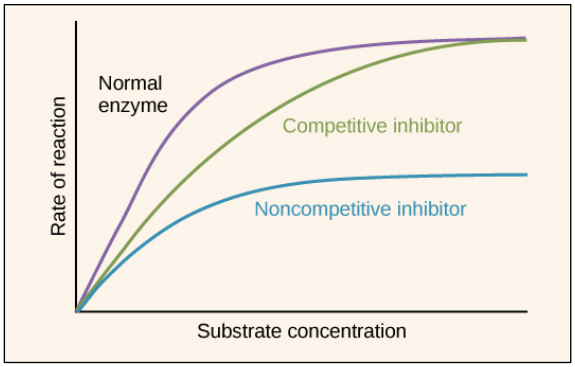


Figure 3: effect of type of inhibition on *maximum* rate of reaction (Khan Academy).

C1.1.16—Regulation of metabolic pathways by feedback inhibition

Use the pathway that produces isoleucine as an example of an end product acting as an inhibitor.

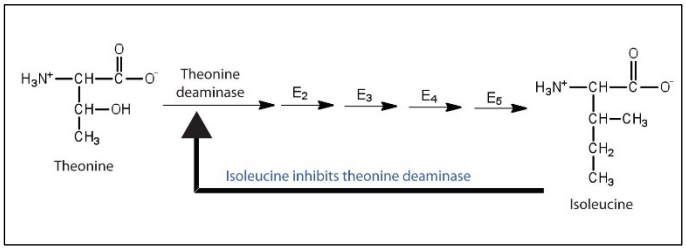


Figure 4: isoleucine end-product inhibition of threonine diagram (Libretexts).

Metabolic pathways can be regulated by **end-product feedback inhibition** in which the last/end product inhibits the enzyme catalyzing the first step of the metabolic pathway. This is done in order to ensure controlled amounts of reactants and products in the pathway; there is enough of each substance but not too much or too little.

For example, the metabolic pathway converting the amino acid threonine into isoleucine is regulated by end-product inhibition. When isoleucine accumulates and is in excess, it noncompetitively inhibits the enzyme threonine deaminase until isoleucine concentrations drop or until threonine amounts are sufficient again.

C1.1.17—Mechanism-based inhibition as a consequence of chemical changes to the active site caused by the irreversible binding of an inhibitor

Use penicillin as an example. Include the change to transpeptidases that confers resistance to penicillin.

Mechanism-based inhibition is an **irreversible** type in which the inhibitor molecule binds permanently to the active site of the enzyme, usually leading to lethal effects.

For example, in gram-positive bacteria, the links between the carbohydrates making up the cell wall are broken to allow the bacteria to grow and expand, then **transpeptidase** cross-links them back together. Penicillin is a mechanism-based inhibitor which binds irreversibly (through a covalent bond) to transpeptidase, preventing the carbohydrates from re-linking. This weakens the cell wall, eventually leading to bursting (lysis).

Linking questions

• What are examples of structure–function relationships in biological macromolecules?

• What biological processes depend on differences or changes in concentration?

Review questions

SL and HL

- State two benefits of catalyzing cellular reactions. [1]
- Outline enzyme specificity. [2]
- Outline two benefits of regulating metabolism in cells. [2]
- Outline the induced-fit theory. [2]
- Outline the benefits of immobilizing enzymes. [3]
- Explain how enzymes catalyze cellular reactions. [3]
- Explain how enzymes interact with other molecules inside cells. [3]
- Distinguish between the two types of metabolic reactions, giving an example for each. [4]
- Discuss the effects of three environmental factors on enzyme activity. [6]

Additional Higher Level

- Describe how statins work. [2]
- Explain how metabolic inefficiency is used for homeostatic regulation in animals. [2]
- Describe how penicillin acts as a mechanism-based inhibitor. [3]
- Distinguish between extracellular and intracellular enzyme reactions, using examples for each. [3]
- An enzyme, A, has a positively charged active site. Explain why its substrate is negatively charged, and suggest the type(s) of inhibition that can occur with negatively-charged substances. [4]
- Describe the process by which an enzyme is synthesized in the cell, starting from translation. [5]
- Distinguish between three types of enzymatic inhibition, using an example for each. [7]

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