C1.1 Enzymes and Metabolism

Guiding Questions

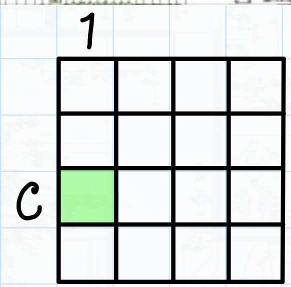
In what ways do enzymes interact with other molecules?

What are the interdependent components of metabolism?

Linking Questions

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

What biological processes depend on differences or changes in concentration?



Theme: Interactions + Interdependence

Level of Organization: Molecules

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Peter Marier

https://www.vmh.life/#reconmap

SL Learning Outcomes

C1.1.1	Enzymes as catalysts	Students should understand the benefit of increasing rates of reaction in cells.
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.
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.
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.
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.
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.
C1.1.7	Relationships between the structure of the active site, enzyme substrate specificity and denaturation	Students should be able to explain these relationships.
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. **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.
C1.1.9	Measurements in enzyme-catalysed reactions	**Application of skills**: Students should determine reaction rates through experimentation and using secondary data.
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 enzymecatalysed reaction. Students should be able to interpret graphs showing this effect.

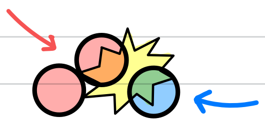
HL Learning Outcomes

C1.1.11	Intracellular and extracellular enzyme-catalysed reactions	Include glycolysis and the Krebs cycle as intracellular examples and chemical digestion in the gut as an extracellular example.
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.
C1.1.13	Cyclical and linear pathways in metabolism	Use glycolysis, the Krebs cycle and the Calvin cycle as examples.
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.
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.
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.
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.

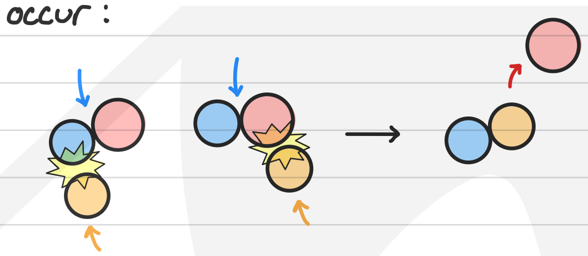
C1.1.1—Enzymes as catalysts. C1.1.4—Enzymes as globular proteins with an active site for catalysis.
C1.1.5—Interactions between substrate and active site to allow induced-fit binding

According to Collision Theory, in order for chemical reactions to occur:

1 There must be a collision

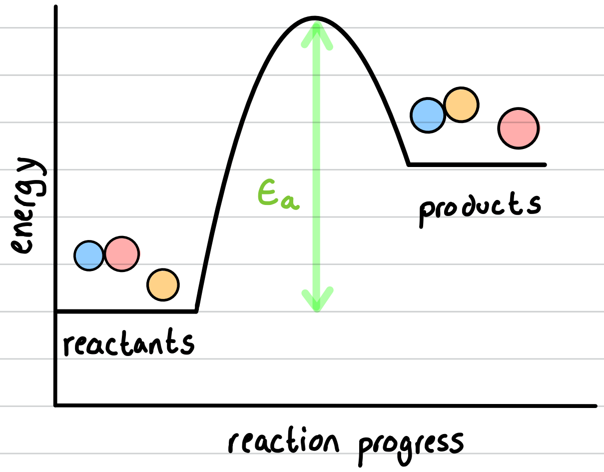


2 The collision must occur at the right location and orientation



3 Collision must occur with sufficient energy

↳ activation energy (E_a): minimum energy required for a reaction to occur



Problem: Chemical reactions unaided take a long time to occur - too long to be able to sustain essential life processes

ex: a study found that some key biological reactions would take hundreds to millions of years to complete! https://pubmed.ncbi.nlm.nih.gov/21495848/

∴ organisms would be long dead before these crucial processes occurred

Solution: enzymes: biological catalysts ↗ from 10^3 to 10^{17} times! ex: an uncatalyzed reaction may take millions of years but catalyzed by an enzyme, a few milliseconds!

↳ substances which increase the rate of reaction, effective in low concentrations and remain unchanged at the end of the reaction (as they don't take part in reactions)

↳ while some enzymes are made of RNA (ex: ribozymes), most are globular proteins; their tertiary structure giving them a rounded shape

Induced-fit model of enzyme action ⟶ analogy:

when a hand enters glove, both change shape

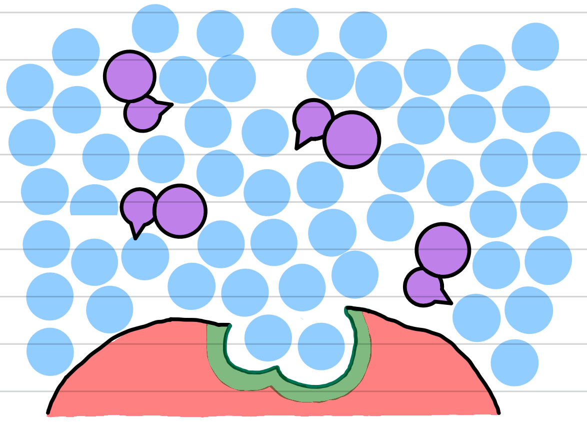
↳ enzymes are substrate-specific, meaning they catalyze (typically) only one particular substrate due to the specific shape of their active site allowing substrate interactions

Definitions

substrate: the reactant in an enzyme-catalyzed reaction

active site: region where substrate binds and catalysis occurs

enzyme-substrate (ES) complex: temporary structure when a substrate and enzyme bind together

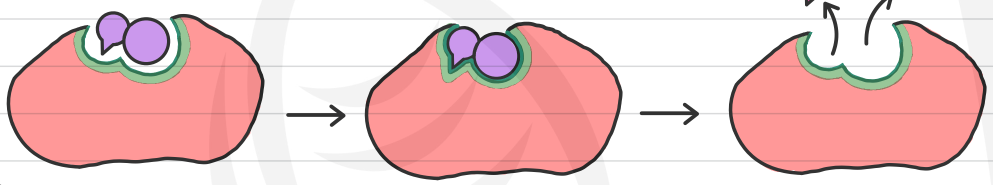


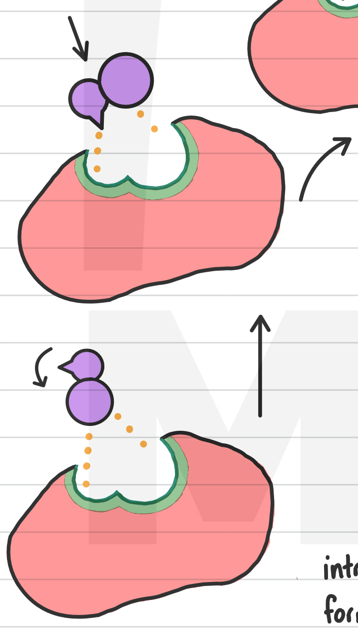
1 most chemical reactions occur in solution where molecules of water, substrate and enzymes are packed close and move around randomly

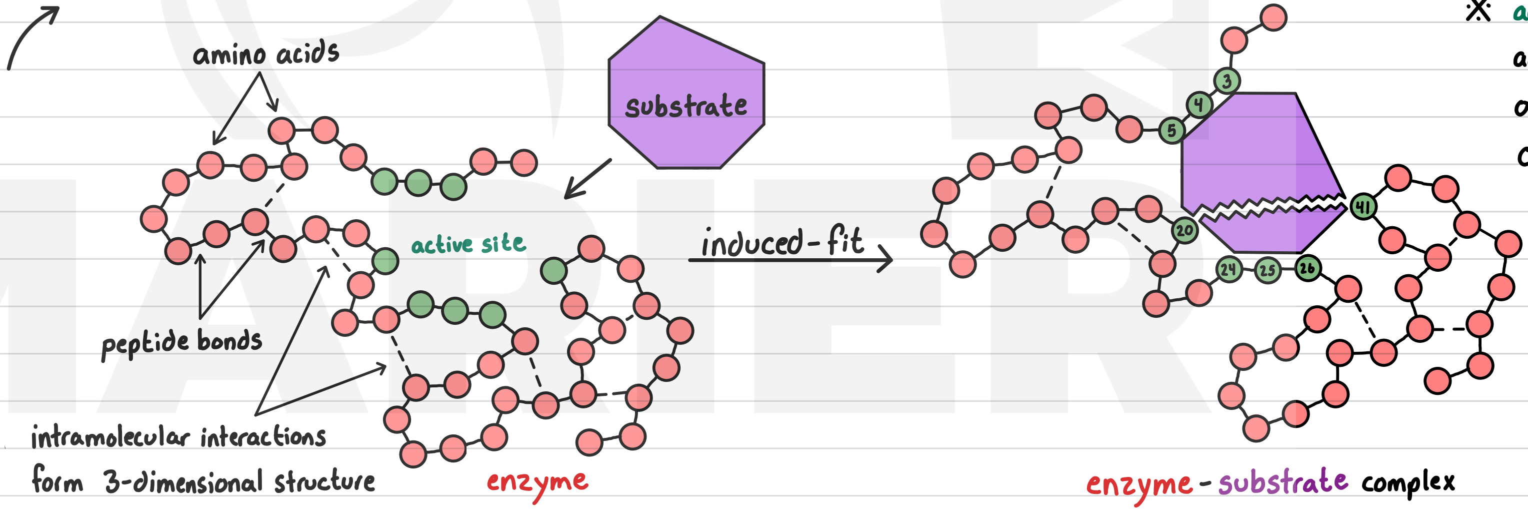
2 When the substrate randomly gets close to the active site, some enzyme's chemical properties draw it closer into the correct orientation

3 As substrate approaches active site, the enzyme's shape conforms to fit the substrate and the substrate's shape also changes to better bind by altering bond angles and shape (induced-fit binding), forming an enzyme-substrate complex. Substrate held in active site by weak interactions (ex: hydrogen bonds)

4 As the substrate is bound, key chemical bonds are stretched/stressed, distorting it and helping it approach the transition state. This reduces the amount of energy needed (E_A) and increases the rate of reaction. Bonds are broken and formed, resulting in product(s). Once released, the enzyme returns to original conformation, ready to be re-used







※ active site is composed of only a few amino acids and are brought together by the folding of the protein. Their interactions enable catalysis and substrate specificity:

↳ some match certain groupings on substrate, allowing ES complex to form and hold substate in place (3-4-5 24-25-26)

↳ some are 'reactive', bringing about a specific catalytic reaction, i.e. building/breaking bonds (20, 41)

Metabolism: complex network of interdependent and interacting chemical reactions occurring in living organisms

↳ interacting: the effect(s) that two or more systems / bodies / substances / organisms have on one another resulting in emergent properties

↳ interdependent: when two or more things depend / rely on each other, such as the activity of enzymes relying on each other in a pathway

extended in HL →

↳ nearly all metabolic reactions are catalyzed by enzymes and many in multi-step pathways where the product of one reaction is the substrate for the next i.e. $A \xrightarrow{\text{enzyme 1}} B \xrightarrow{\text{enzyme 2}} C \xrightarrow{\text{enzyme 3}} D \xrightarrow{\text{enzyme 4}} E$

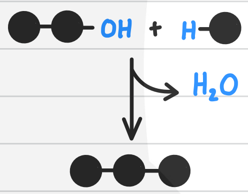
↳ this allows a reaction to be precisely regulated (as a different enzyme required at each step) and the energy involved better-controlled (as it can be incrementally released and used rather than all at once)
- ↳ cells can direct specific reactions by synthesizing specific enzymes or blocking them, giving them control
- ↳ this requires organisms to make many different enzymes

ex: if cellular respiration occurred in one step it would be combustion!

※ enzymes are typically named after their substrate + 'ase' ex: lactase breaks down lactose

Metabolic reactions can be classified as either anabolic or catabolic

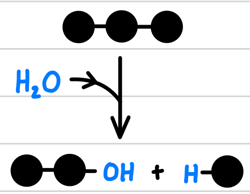
Anabolism: synthesis of complex, larger molecules from simpler, smaller molecules



↳ formation of macromolecules from monomers by condensation reactions

examples:
- synthesis of proteins from amino acids (translation) 🔗 proteins B1.1 🔗 protein synthesis D1.2
- synthesis of polysaccharides from monosaccharides (ex: glucose into glycogen) 🔗 carbohydrates B1.1
- synthesis of DNA from nucleotides 🔗 nucleic acids A1.2 🔗 DNA replication D1.1
- photosynthesis 🔗 photosynthesis C1.3

Catabolism: breakdown of larger complex molecules into simpler, smaller molecules

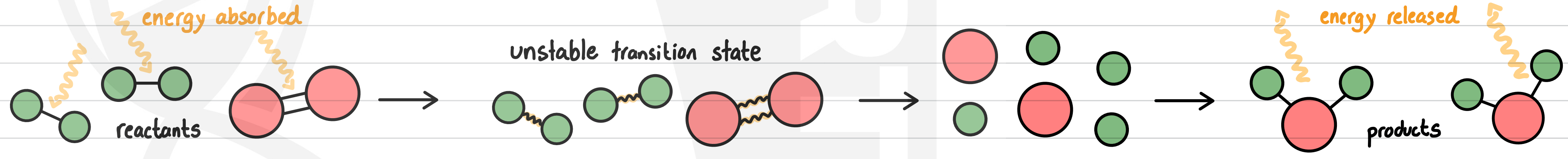


↳ formation of monomers from macromolecules by hydrolysis reactions

examples:
- hydrolysis of macromolecules into monomers in digestion (in mouth, stomach, intestines)
- oxidation of substrates in cellular respiration 🔗 cell respiration C1.2
- digestion of complex carbon compounds from dead organic matter by decomposers 🔗 transfers of energy and matter C4.2

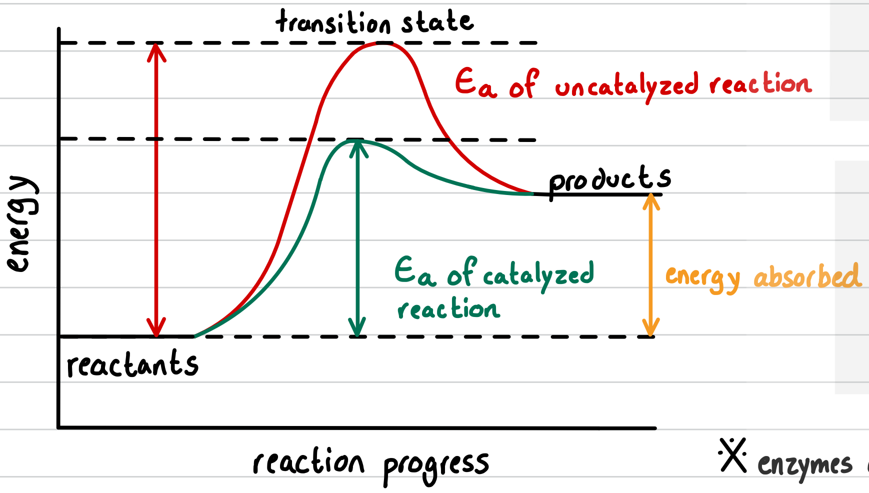
Chemistry review

In chemical reactions, the bonds holding reactants together need to break, which requires energy while forming new bonds in the products releases energy



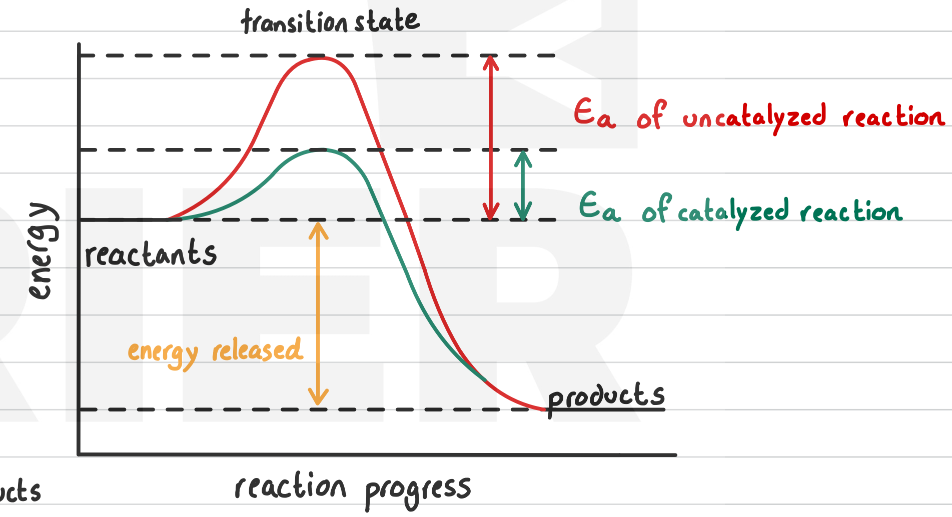
↳ anabolic reactions are **endergonic**: energy used to break bonds > energy released from forming bonds
∴ products have more energy than reactants (taken from surroundings)

↳ catabolic reactions are **exergonic**: energy used to break bonds < energy released from forming bonds
∴ reactants have more energy than products (released to surroundings)

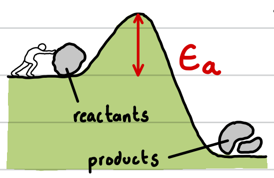


- Activation energy (E_a) is needed to reach the transition state, i.e. break the bonds holding reactants together.
- Enzymes lower the E_a through binding with substrate at the active site which destabilizes these bonds, making it easier to reach transition state and initiate reaction

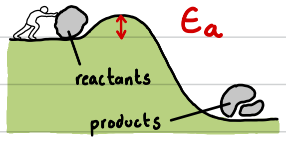
※ enzymes do not provide or alter energy levels of reactants or products



- analogy: boulder on hillside



the boulder needs to be pushed up a hill in order to break

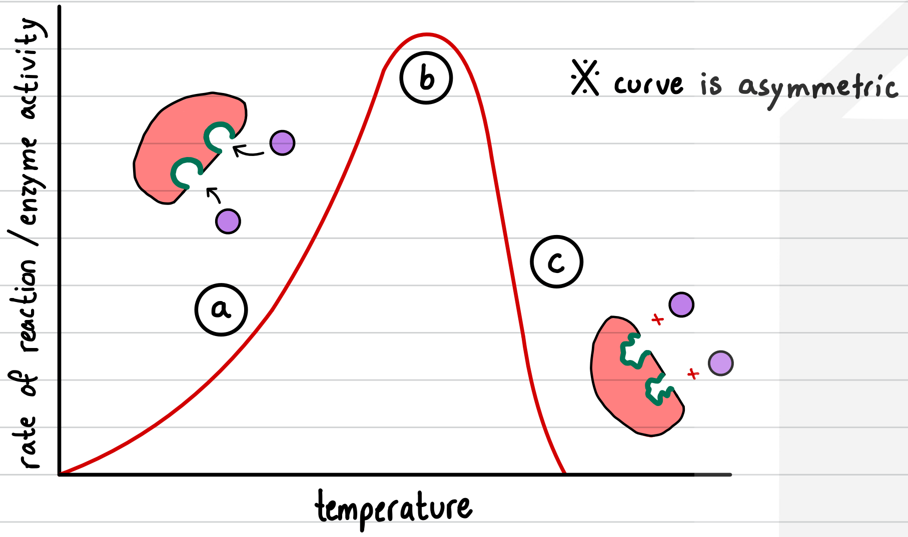


enzyme lowers the hill so less pushing needed

Enzyme activity (how effectively/quickly enzymes catalyze substrates into products) is impacted by many factors, namely: temperature, pH, and substrate concentration

Effect of temperature

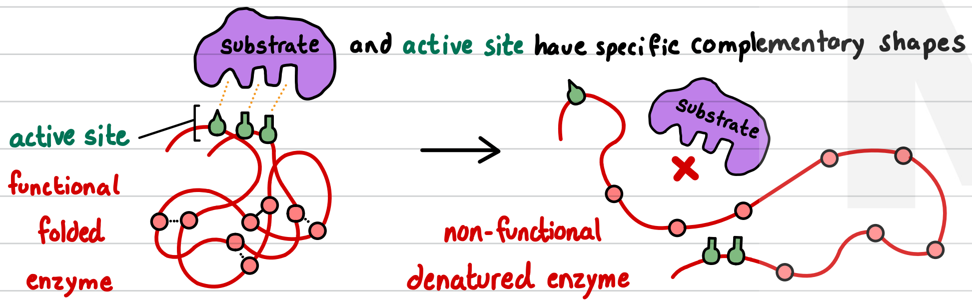
recall: temperature is a measure of average kinetic energy



(a) as temperature rises, particles have more kinetic energy, meaning they are moving randomly faster
↳ more frequent and stronger collisions between substrates and the active site of enzymes
↳ more reactions catalyzed over time, i.e. higher enzyme activity

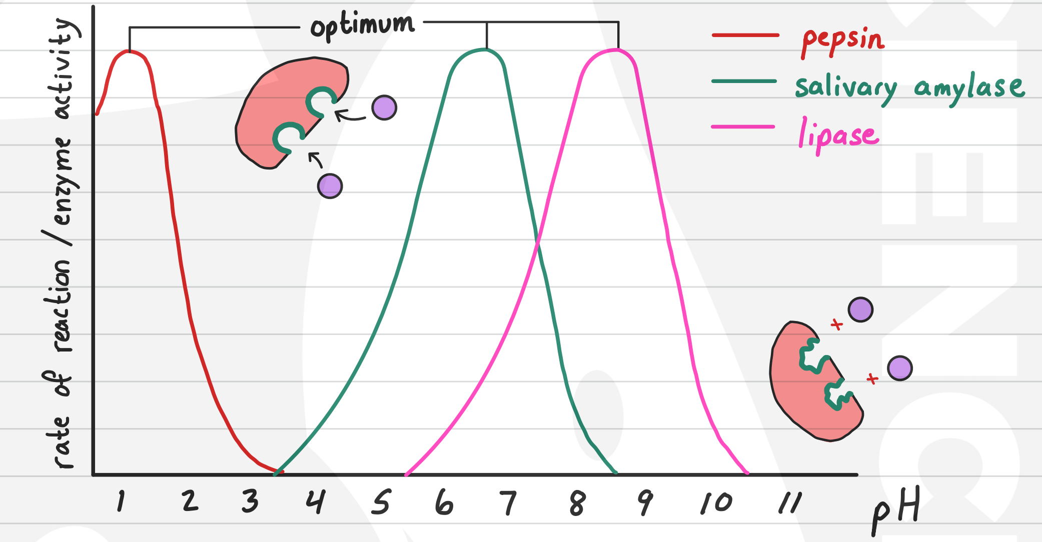
(b) optimum temperature: temperature at which enzyme activity is at its maximum
↳ will depend on the enzyme and its particular intramolecular bonds
ex: most enzymes in humans have an optimum ~37°C

(c) increasing temperature beyond the optimum temperature the enzyme's intramolecular bonds are disrupted, causing it to denature
↳ its 3-dimensional conformation and thus, the shape of its active site is altered, preventing substrate from binding
↳ reaction no longer catalyzed thus despite more energy, rate declines



Effect of pH

recall: pH is a logarithmic measure of acidity/alkalinity of a substance



Different enzymes have different amino acid sequences and thus different intramolecular interactions, 3-dimensional shapes, and optimum pH

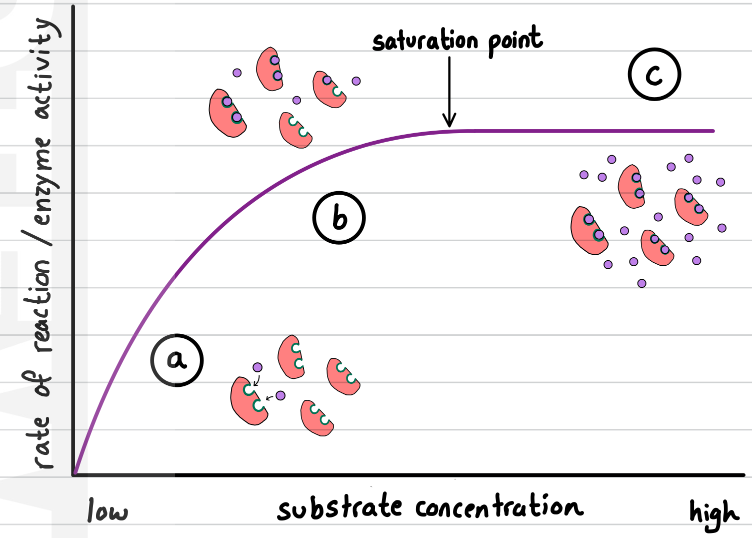
↳ too acidic (more H^+ in solution) or too alkaline (more OH^- in solution) can disrupt the intramolecular forces such as ionic and hydrogen bonds by altering charges of groups.
↳ This can result in the protein denaturing, altering the shape of its active site, preventing substrate(s) from binding, lowering enzyme activity and reaction rate

Examples — proteins B1.1

- pepsin is an enzyme which catalyzes breakdown of proteins in the stomach - optimum is very acidic
- salivary amylase is an enzyme which catalyzes breakdown of starch in the mouth - optimum is ~neutral
- lipase is an enzyme which catalyzes breakdown of lipids in the small intestine - optimum is alkaline

Effect of substrate concentration

Concentration: amount of solute per volume, expressed as $mol\,L^{-1}$ or %

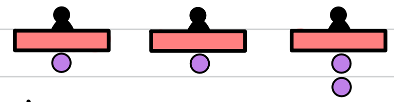


(a) at low substrate concentrations, there are many free active sites, meaning substrates can bind readily without delay (excess of enzymes)
↳ increasing the substrate concentration will proportionally increase rate of reaction as more substrates will collide with the enzyme's active site, forming enzyme-substrate complexes and be catalyzed

(b) as substrate concentration increases, the increase in rate diminishes as more of the active sites at a given time are occupied
∴ likelihood of a substrate colliding with a free active site decreases

(c) at high substrate concentrations, a further increase has no effect on the rate of reaction as all enzyme active sites are occupied and the rest of the substrates "need to queue" as they cannot bind yet
↳ saturation point: enzymes all occupied and working at max efficiency

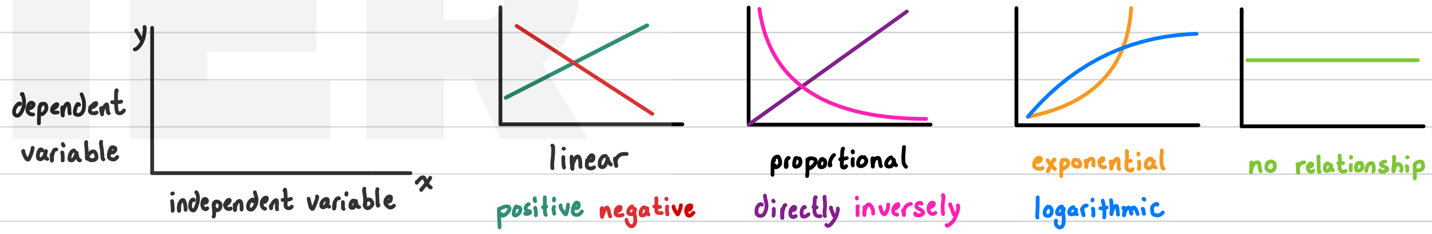
- analogy: ticket windows (enzyme) customer (substrate)



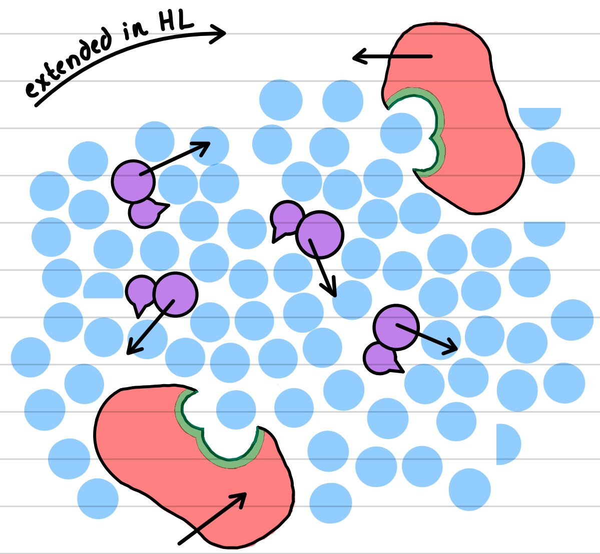
only 3 customers can be helped at max

NOS:

- graphs are a visual representation of data, allowing patterns and relationships to be seen easier
- generalized graphs are models which can be evaluated using experiments



In living organisms nearly all chemical reactions occur in solutions - whether inside cells (cytoplasm, organelles, vesicles) or outside (interstitial fluid, blood plasma) water A1.1



recall: in order for an enzyme-catalyzed reaction to occur, the substrate must collide at the right orientation and with sufficient energy at the enzyme's active site

↳ as both substrates and enzymes are moving randomly in solutions, increasing collision likelihood is crucial

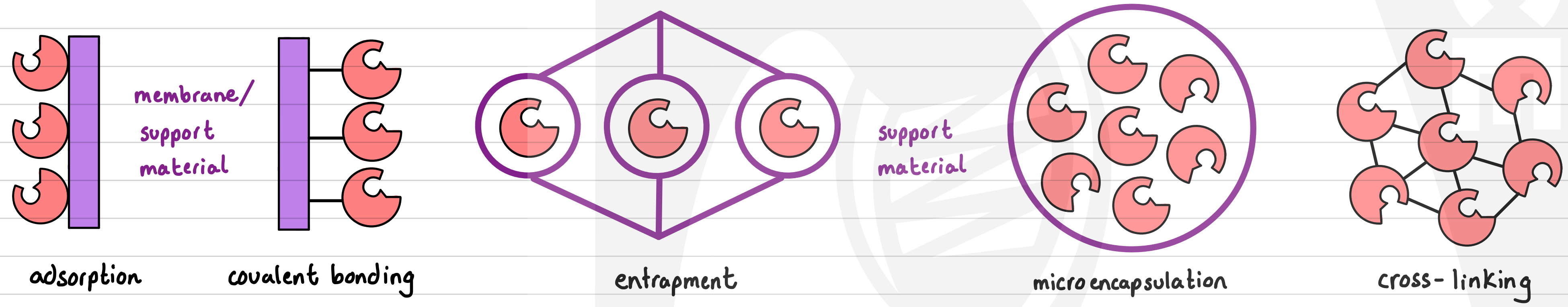
↳ increasing temperature provides more kinetic energy and increases collision likelihood, but it cannot be raised too high as enzymes will denature and stop functioning

↳ increasing enzyme concentration would be beneficial but this requires additional resources

solution: immobilization

immobilized enzyme: an enzyme attached to an inert, insoluble material → this is beneficial as it improves enzyme stability and can provide a better environment for enzyme activity

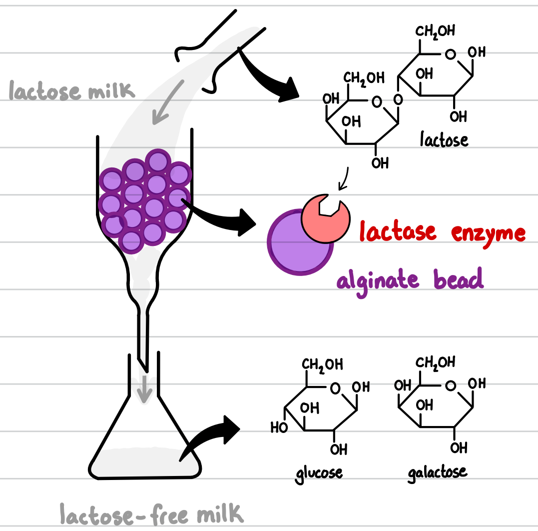
↳ enzymes can be immobilized in a number of ways:



※ sometimes large substrate molecules can be immobilized similarly for better efficiency

↳ immobilized enzymes are frequently used in industry

ex: the production of lactose-free milk:



milk containing lactose is passed repeatedly through a funnel containing lactase immobilized on beads.

lactase breaks down lactose into glucose and galactose, producing lactose-free milk. As lactase is immobilized it is not in the final product and can be easily re-used

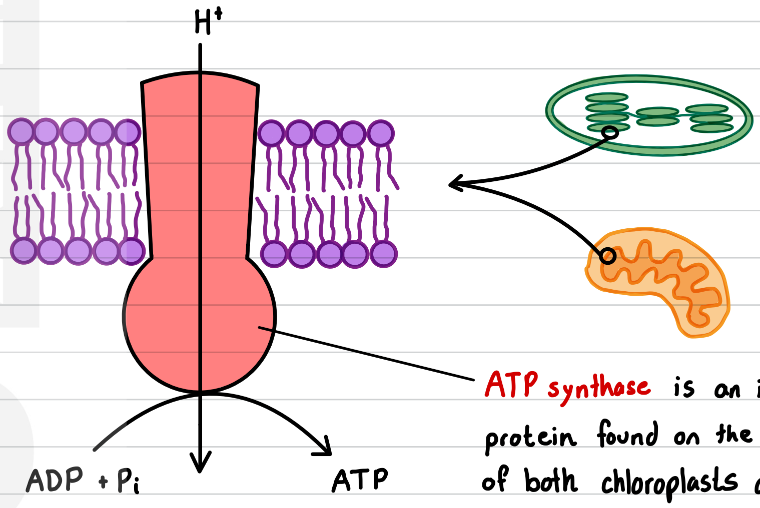
※ advantages to using these in industry:

- ✓ enzymes easily separated from product
- ✓ enzymes retrieved easier for re-use
- ✓ enzymes stable at higher temperatures without denaturing
- ✓ enzymes can be used at higher concentrations

other examples of immobilized enzyme use:

- production of gluten-free beer
- production of penicillin and other antibiotics
- production of ethanol biofuels
- diagnosis of diseases
- cleaning textiles

↳ immobilized enzymes are used in key metabolic processes:



cell respiration C1.2
photosynthesis C1.3

ATP synthase is an integral protein found on the membrane of both chloroplasts and mitochondria and is essential in photosynthesis and aerobic cell respiration

Measuring rates of chemical reactions

reactant (s) $\xrightarrow{\text{enzyme}}$ product (s)

larger change = faster rate

measure how much reactant / substrate is being consumed over a given time period

$\frac{\Delta \text{reactant}}{\text{time}} = \frac{\text{final} - \text{initial}}{\text{time}}$

↳ measurement options for reactants (substrates):

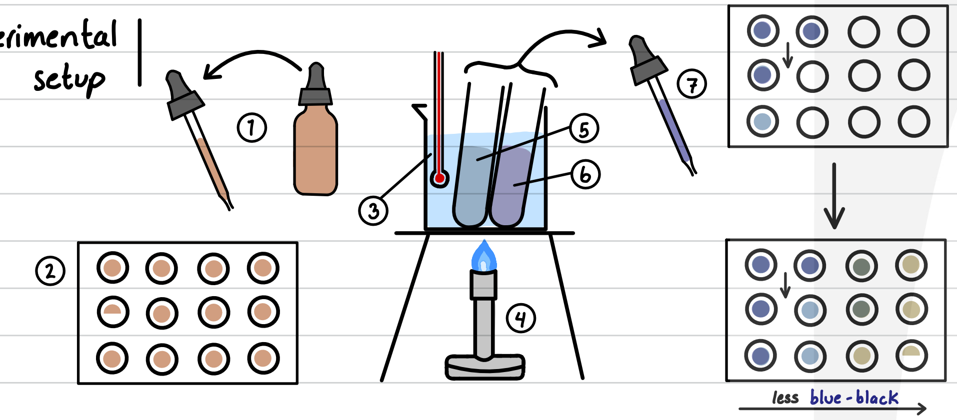
- change in pressure of sealed container or concentration of substrate (if its a gas)
- % change in mass of substrate (if its a solid)
- change in diameter of substrate-infused agar cubes
- colour change using substrate-specific indicator as substrate converted to product

* iodine-KI : yellow-brown → blue-black in presence of starch

↳ example experiment: starch $\xrightarrow{\alpha\text{ amylase}}$ maltose

RQ: How does pH or temperature or substrate concentration impact α amylase activity as measured by change in colour over time (s) using iodine-KI solution as an indicator?

experimental setup



① dropper with iodine-KI reagent
② spotting tile
③ beaker with water and thermometer
④ bunsen burner to heat water
* alternative: water bath
⑤ solution: starch
⑥ solution: amylase + pH buffer
⑦ dropper with mixed solution

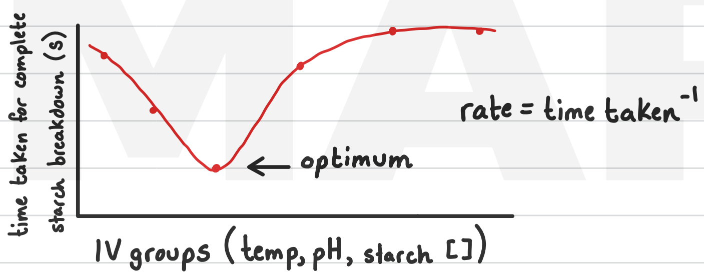
methodology summary

1- IV chosen and range selected (ex: starch concentration 0%, 1%, 2%, 3%), rest kept constant
2- use dropper to place drop of iodine-KI in spotting tile wells
3- create solution of amylase and add to test tube A. Add desired pH buffer. Place in heated water
4- create solution of starch and add to test tube B. Bring to temperature. Mix A and B. Start timer.
5- using a dropper, drop solution on a well containing iodine-KI solution at set time increments (ex: every 20 seconds). Record colour of solution in well
6- continue until colour is yellow-brown (no more starch). Repeat for more trials and at different IV groups

* a great alternative is spectrophotometry as it allows precise, quantitative data

data

IV groups	time until yellow-brown (s) T1	T2	T3	T4	T5



measure how much product is being made over a given time period

$\frac{\Delta \text{product}}{\text{time}} = \frac{\text{final} - \text{initial}}{\text{time}}$

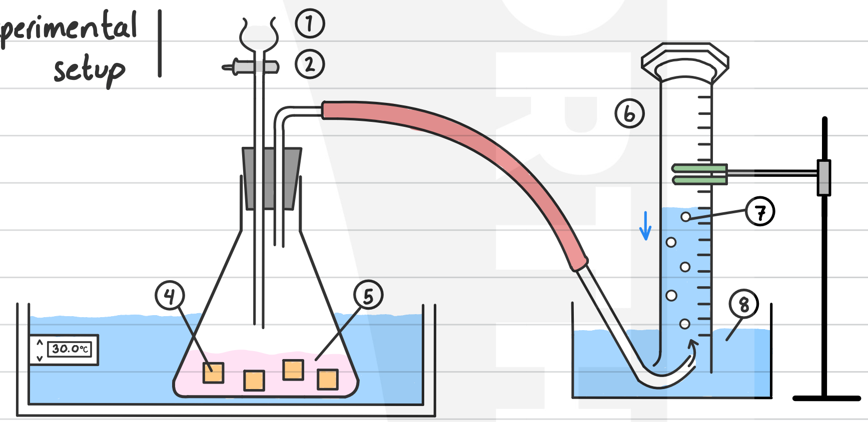
↳ measurement options for products:

- counting bubble formation (if product is gas)
- colour change using product-specific indicator as substrate converted to product
- change in pressure of sealed container or concentration of product (if its a gas)
- time for enzyme-soaked disc to rise in substrate solution (if its a gas)
- diffusion out of dialysis tube (if product is permeable but substrate is not)
- displacement of water or syringe (if product is gas)

↳ example experiment: hydrogen peroxide $\xrightarrow{\text{catalase}}$ oxygen + water

RQ: How does pH or temperature or substrate concentration impact catalase activity in potatoes as measured by oxygen gas production (cm^3) over time (s)?

experimental setup



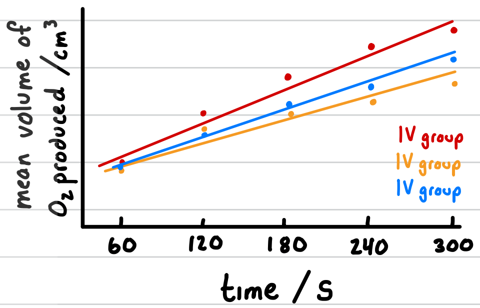
① reservoir contains substrate H_2O_2
② stopcock controls flow from reservoir
③ electronic water bath regulates temperature
④ source of catalase (potatoes, liver, kidney, seeds)
⑤ pH buffer solution – controls pH
⑥ graduated cylinder – measures O_2 volume
⑦ O_2 bubbles produced
⑧ water – excludes air during O_2 collection
* alternative: digital O_2 sensor

methodology summary

1- IV chosen and range selected (ex: temperature 20, 30, 40, 50 °C), rest kept constant
2- release H_2O_2 and start timer. Consistently stir/shake flask
3- at set time-increments (ex: every 20 seconds) record water level (cm^3) on graduated cylinder
4- continue for desired length (ex: 300 seconds). Repeat for more trials and at different IV groups

data

time s (± uncertainty)	volume of O_2 produced cm^3 (± uncertainty)
20	
40	
60	
80	

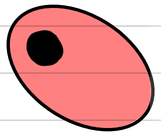


rate can be calculated from LOBF and data

$= \frac{\Delta O_2 \text{ production}}{\Delta \text{ time}} \frac{cm^3}{s}$

HL C1.1.11—Intracellular and extracellular enzyme-catalysed reactions. C1.1.12—Generation of heat energy by the reactions of metabolism. C1.1.13—Cyclical and linear pathways in metabolism

Enzymes catalyze reactions both inside cells and outside of cells

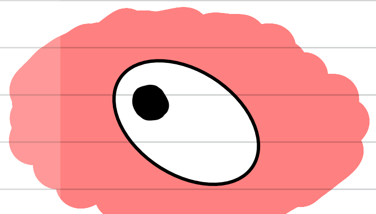


Intracellular enzymes (endoenzymes)

- remain in the cell after synthesis
- majority of enzymes
- work on substrates within cells
- functions include cellular metabolism, both anabolic and catabolic

examples:

- enzymes in nucleus: DNA polymerase, DNA helicase, DNA ligase, DNA primase, RNA polymerase (DNA replication D1.1)
- enzymes in cytoplasm: enzymes in glycolysis - hexokinase (cell respiration C1.2)
- hydrolytic enzymes in lysosomes: proteases, lipases, amylase, etc. (disease defence C3.2)
- enzymes in mitochondria: ATP synthase (inner membrane), enzymes in Krebs cycle - fumarase (matrix) (cell respiration C1.2)
- enzymes in chloroplasts: ATP synthase (thylakoid membrane), enzymes in Calvin cycle – RuBisCo (stroma) (photosynthesis C1.3)



Extracellular enzymes (exo enzymes)

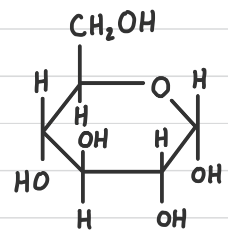
- secreted out of cells via exocytosis after synthesis
- minority of enzymes
- work on substrates outside cells
- functions typically catabolic, acting on larger substrates and breaking them down

examples:

- enzyme secreted by skin and eyes: lysozyme (disease defence C3.2)
- enzyme secreted in mouth: salivary amylase
- enzyme secreted in stomach: pepsin
- enzymes secreted in intestines: trypsin, lipase, pancreatic amylase

The conversion of energy from one form to another is never 100% efficient as some energy is always converted as heat (due to the Second Law of Thermodynamics)

- in exergonic reactions, such as the oxidation of glucose in cell respiration, much energy is released
- while heat or thermal energy cannot be converted to free energy and used directly by organisms, it can still be utilized as a heat source in endotherm animals who rely on it for thermoregulation
  ex: all mammals and birds (and some other animals) use the heat generated from respiration to help maintain a constant internal body temperature. Human brown adipose tissue can undergo uncoupled respiration where all energy is released as heat as a way to boost this process (homeostasis D3.3)



+ 6 O=O → → → → → → → 6 O=C=O + 6 H_2O

most is lost as heat energy

the goal is to store this energy as free energy in the molecule ATP where it can be used (cell respiration C1.2)

ADP + P_i → ATP

metabolic pathway: sequence of enzyme-catalyzed biochemical reactions occurring in organisms

- substrates are converted into intermediates in a chain of small sequential reactions until final product is produced

analogy: conversion of TREAD into BLINK by only changing only one letter at a time to make a real word

initial substrate: TREAD → BREAD → BREED → BLEED → BLEND → BLIND → BLINK (product)

intermediates: BREAD, BREED, BLEED, BLEND, BLIND

- Metabolic pathways typically fall into 1 of 2 types:

① **linear pathway**: series of enzyme-catalyzed reactions which run in one direction from reactant to product

initial substrate $\xrightarrow{\text{enzyme 1}}$ intermediate product A $\xrightarrow{\text{enzyme 2}}$ intermediate product B $\xrightarrow{\text{enzyme 3}}$ final product

※ metabolism is usually not this simple but a complex web of both

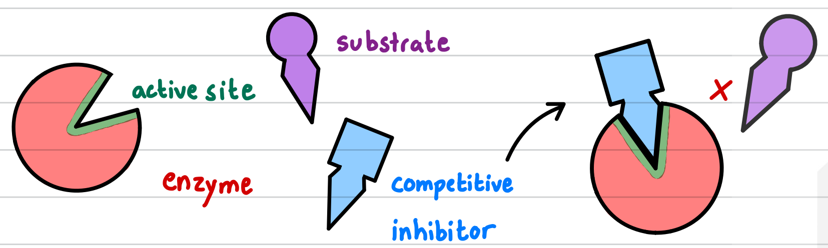
ex: cellular respiration has both linear pathways (glycolysis) and cyclical pathways (Krebs cycle). Light-independent reactions of Photosynthesis is the Calvin cycle

② **cyclical pathway**: circular series of enzyme-catalyzed reactions where there is no end, the initial substrate being eventually reformed

initial substrate $\xrightarrow{\text{enzyme 1}}$ intermediate product A $\xrightarrow{\text{enzyme 2}}$ intermediate product B $\xrightarrow{\text{enzyme 3}}$ intermediate Product C $\xrightarrow{\text{enzyme 4}}$ initial substrate

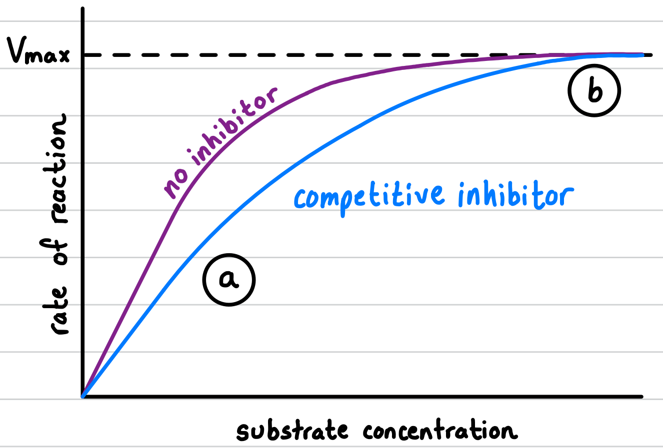
Enzyme activity can be reduced or halted entirely by the binding of inhibitors (typically reversibly). There are two major types: competitive and non-competitive

Competitive inhibitors: compete directly with the substrate and bind to the enzyme's active site blocking substrate from binding



↳ competitive inhibitor is structurally and chemically similar to the substrate allowing it to form similar interactions and bind to the enzyme's active site, blocking the substrate and preventing catalysis

Effect on enzyme activity



(a) rate of reaction is reduced as inhibitor competes with substrate, reducing successful enzyme-substrate complexes and catalysis - lowering enzyme affinity. Increasing the substrate concentration increases likelihood of enzyme binding with it rather than inhibitor

(b) Maximum rate of reaction (Vmax) is achieved as the concentration of substrate is so high that the likelihood of enzyme's binding to them overcomes inhibition

Example - Statins

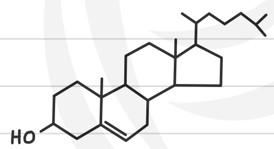
transport B3.2

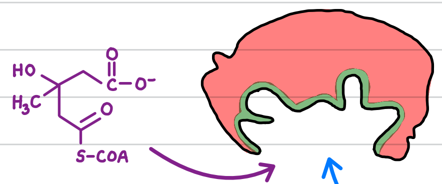
↳ Statins are medicines that are used to treat high blood cholesterol - a contributor to heart disease

↳ They function as competitive inhibitors to HMG-CoA reductase, reducing the liver's production of cholesterol

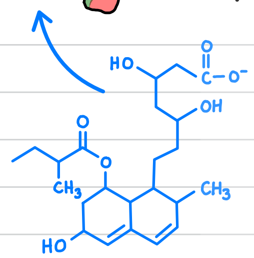
↳ Cholesterol is the product of a linear metabolic pathway:

A ⟶ B ⟶ HMG-CoA $\xrightarrow{\text{HMG-CoA reductase}}$ D ⟶ E ⟶ cholesterol





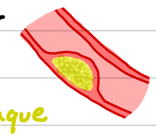
the enzyme HMG-CoA reductase binds to and catalyzes HMG-CoA conversion in the pathway



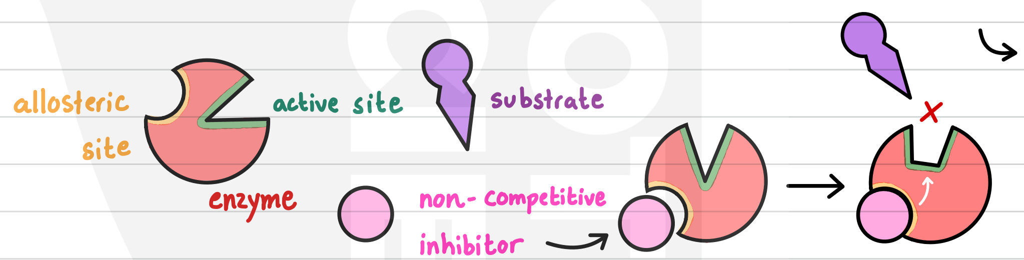
due to their similar shape, the molecule group statins competes with HMG-CoA and can also bind to the active site of HMG-CoA reductase, reducing the rate of reaction and ultimately the amount of cholesterol being produced

※ two forms of cholesterol in blood:
- HDL - collects excess in blood
- LDL - delivers from liver

∴ if LDL >> HDL, cholesterol builds up and can form plaque

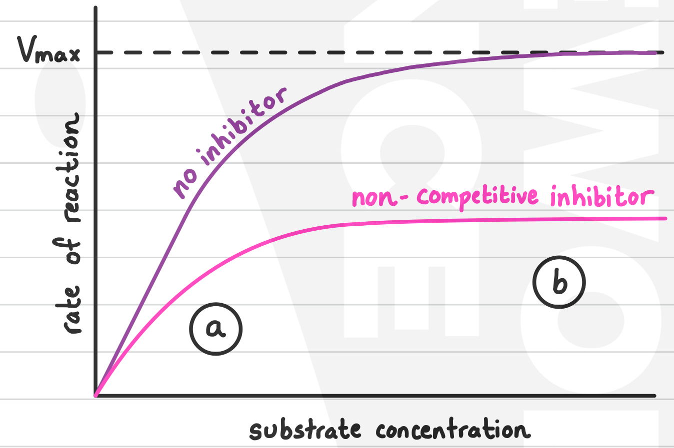


Non-competitive inhibitors: bind to an enzyme's allosteric site (not active site), causing a change to the active site, preventing a substrate from binding



↳ non-competitive inhibitor binds to the allosteric site, altering interactions within the enzyme, leading to a conformational change to the active site preventing the substrate from successfully binding for as long as it is bound

Effect on enzyme activity



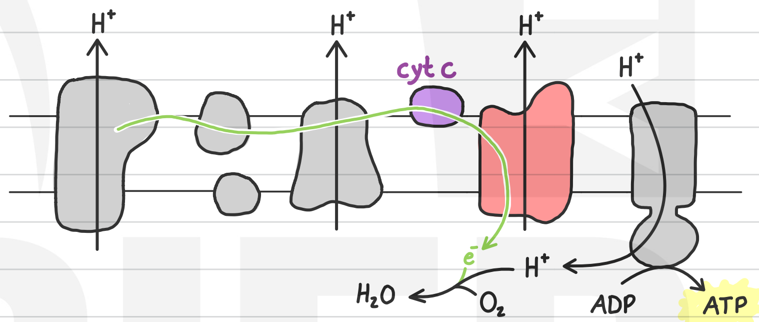
(a) rate of reaction is reduced as inhibitor alters the active site and disables some enzymes, causing fewer able to catalyze substrate reactions. Enzyme affinity unaltered as uninhibited enzymes function just as well

(b) Maximum rate of reaction (Vmax) achieved is far lower than uninhibited as adding more substrates cannot overcome enzymes which are disabled/inactive as they do not compete with inhibitors for the allosteric site

Example - Cyanide poisoning

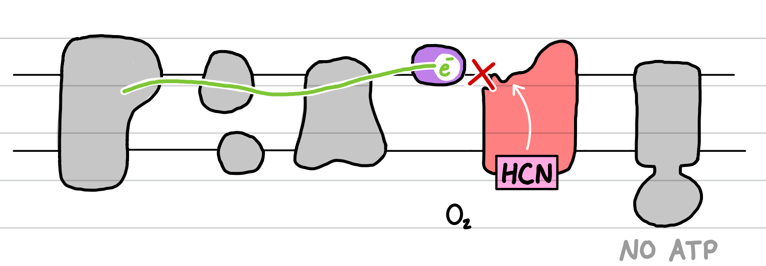
↳ Cyanides, such as Hydrogen Cyanide $\boxed{HCN}$ are very potent poisons which if ingested or inhaled may be fatal as it halts oxidative phosphorylation during aerobic respiration in mitochondria.

↳ It acts as a non-competitive inhibitor to cytochrome c oxidase (Complex IV) in the electron transport chain



normally, in aerobic cell respiration, cytochrome c oxidase removes electrons from cytochrome c and puts them onto O_2 to form water. This process allows H^+ to be pumped into intermembrane space in order to diffuse through ATP synthase and produce ATP

cell respiration C1.2

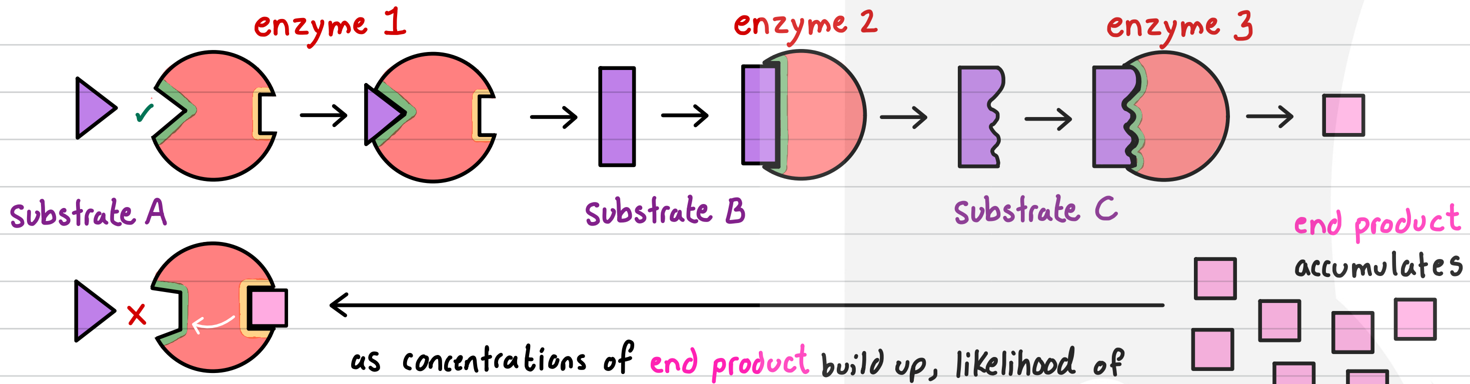


Cyanide binds to an allosteric site of cytochrome c oxidase causing a conformational change, inhibiting electron transfer from cytochrome c. This halts the electron transport chain, preventing water formation, proton gradient formation, and the production of ATP aerobically, leading to death

C1.1.16—Regulation of metabolic pathways by feedback inhibition. C1.1.17—Mechanism-based inhibition as a consequence of chemical changes to the active site caused by the irreversible binding of an inhibitor

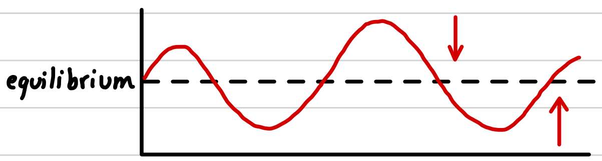
Many metabolic pathways are not always active and making products as this may produce an overabundance of product and waste materials and energy
↳ instead they are regulated by the process of feedback or end-product inhibition

Feedback inhibition: when the end-product of a metabolic pathway acts as an inhibitor to the initial enzyme in the pathway, thus halting its own production
↳ end product acts like a non-competitive inhibitor and binds to the allosteric site of the first enzyme, altering its active site and disabling it



as concentrations of end product build up, likelihood of inhibition increases and pathway slowed, making less end product

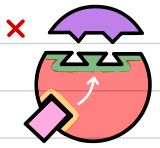
This is an example of **negative feedback**: feedback that tends to counteract any deviation from equilibrium and promotes stability. Very common in homeostatic controls
where if a system moves from set point, changes occur to reduce and reverse this change in order to maintain steady-state
ex: blood glucose and temperature regulation



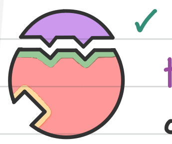
homeostasis D3.3

Example - threonine-isoleucine pathway

↳ Bacteria (but not humans) can synthesize the amino acid isoleucine from threonine in a metabolic pathway



threonine
threonine deaminase
↓
intermediate A
↓ enzyme 2
intermediate B
↓ enzyme 3
intermediate C
↓ enzyme 4
intermediate D
↓ enzyme 5
isoleucine

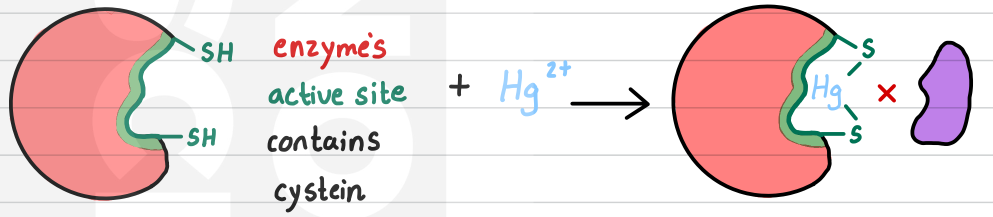


threonine binds to active site of threonine deaminase and it is catalyzed into intermediate ultimately producing isoleucine
↑
allosteric site (largely) unoccupied
↑
isoleucine concentration decreases
↑
isoleucine (end product) being used for protein synthesis

isoleucine (end product) accumulates
↑
isoleucine concentration increases
↑
isoleucine bound to allosteric site of threonine deaminase
↑
active site's conformation altered, preventing threonine from binding and halting pathway

↳ Some inhibitors, such as heavy metals (ex: mercury) or nerve agents (ex: Sarin) bind irreversibly to the active site of enzymes by forming strong covalent bonds with SH residues, which can be fatal

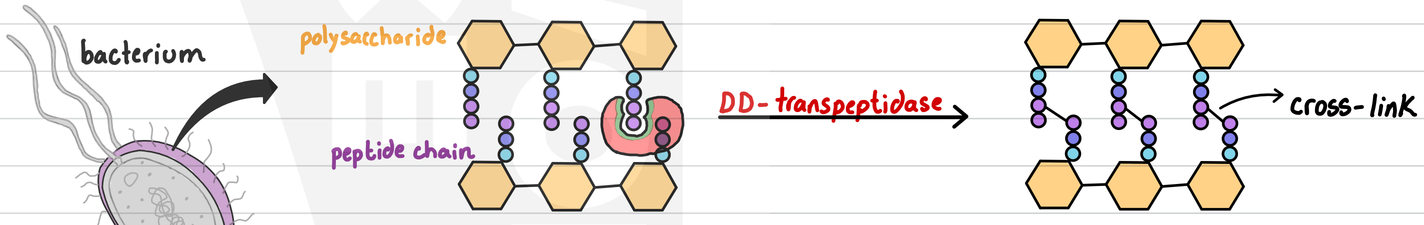
ex: mercury poisoning



Mechanism-based inhibition (aka suicide inhibitors): when unreactive molecules are activated through catalytic reactions, causing irreversible enzyme inhibition

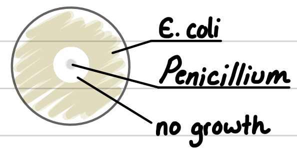
↳ These types of inhibitors are specific to a certain enzyme (their shape is similar to the substrate) allowing them to bind to the active site. Once bound, they are modified by the enzyme into a reactive group which forms a covalent bond with enzyme resulting in a permanent inhibitor-enzyme complex

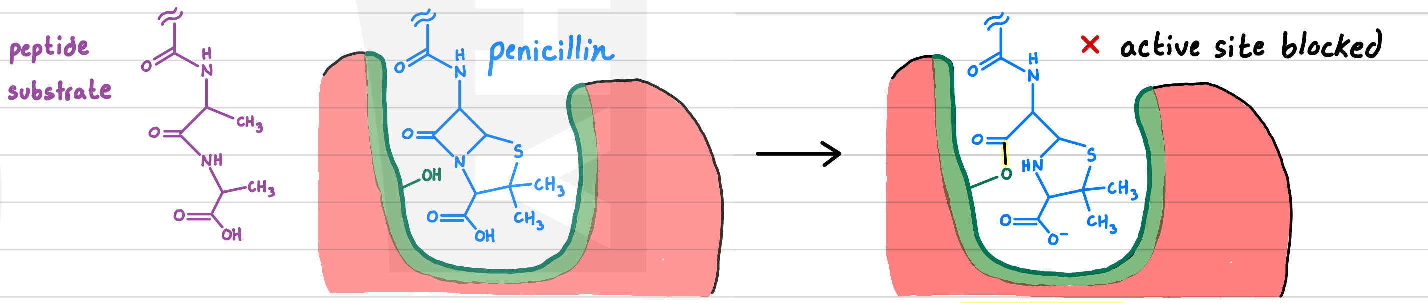
Example - penicillin antibiotic



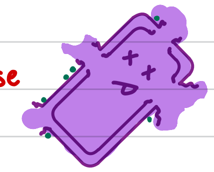
cross-links between peptide chains are catalyzed by transpeptidase enzymes to form the peptidoglycan cell wall in bacteria. Cell wall is crucial for cellular structure and protection

↳ Penicillin is a group of antibiotic chemicals obtained from *Penicillium* moulds
↳ they have a very similar shape to the terminal ends of the peptide chains, allowing them to bind in the active site of transpeptidase instead of the peptide substrate





↳ Penicillin enters active site and is subsequently modified, forming covalent bond with the enzyme. This bond is irreversible; blocking the active site and inactivating transpeptidase
↳ as peptidoglycan synthesis is halted, bacterial cell wall is compromised, which causes cell to be unable to maintain osmotic pressure, leading to cell lysis and death



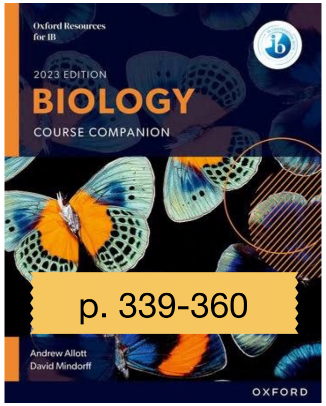
disease defence C3.2

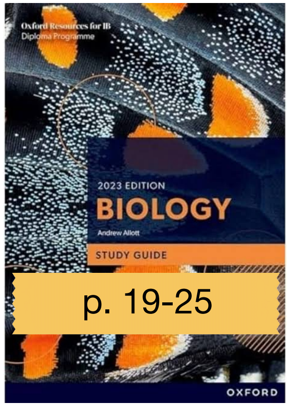
※ some bacterial strains have become resistant to antibiotics through mutations. One mutation caused the shape of the transpepsidase active site to change, reducing penicillin's affinity or even ability to bind

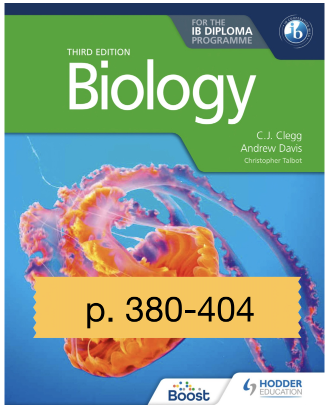
Resource Links

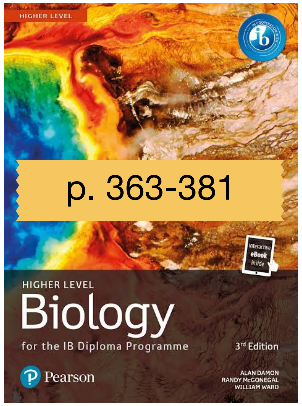
each resource is hyperlinked

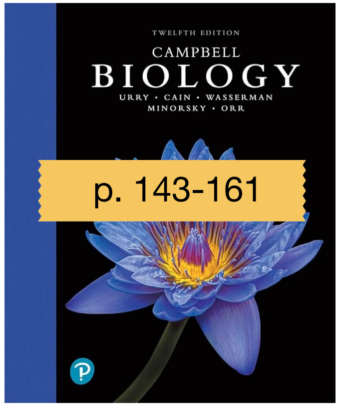
Textbooks



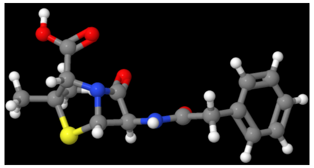




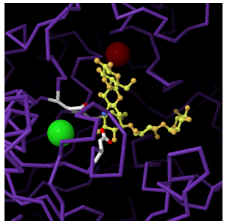




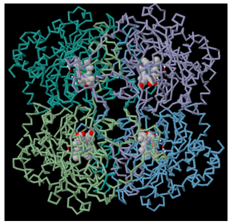
3D models



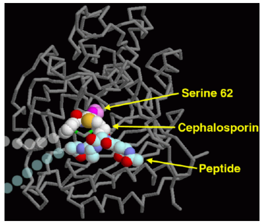
Penicillin G



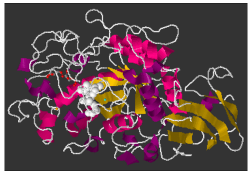
Alpha-amylase



Catalase



Penicillin-binding proteins



Amylase

Articles

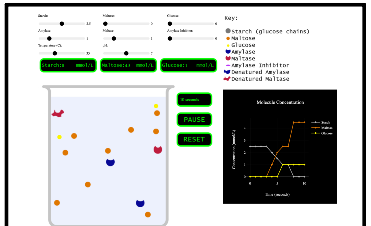
Bansal, A. B. (2023, July 3). HMG-COA reductase inhibitors. StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK542212/

Knowles, J. R. (1985). Penicillin resistance: the chemistry of .beta.-lactamase inhibition. Accounts of Chemical Research, 18(4), 97–104. https://doi.org/10.1021/ar00112a001

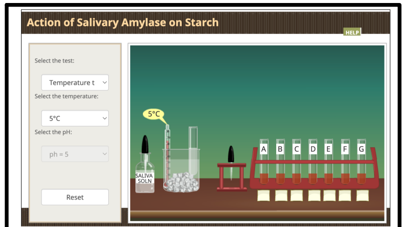
Maghraby, Y. R., El-Shabasy, R. M., Ibrahim, A. H., & Azzazy, H. M. E. (2023). Enzyme immobilization Technologies and industrial Applications. ACS Omega, 8(6), 5184–5196. https://doi.org/10.1021/acsomega.2c07560

Wolfenden R. (2011). Benchmark reaction rates, the stability of biological molecules in water, and the evolution of catalytic power in enzymes. Annual review of biochemistry, 80, 645–667. https://doi.org/10.1146/annurev-biochem-060409-093051

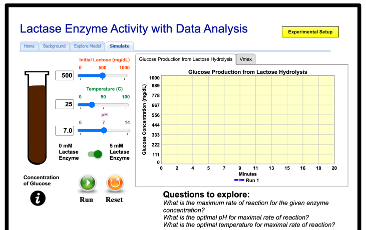
Simulators / Interactives



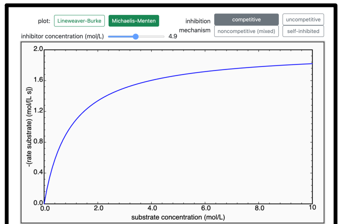
Factors affecting enzymes



Action of salivary amylase



Lactase enzyme activity



Enzyme inhibition