DP IB Biology: HL

Your notes

8.1 Metabolism

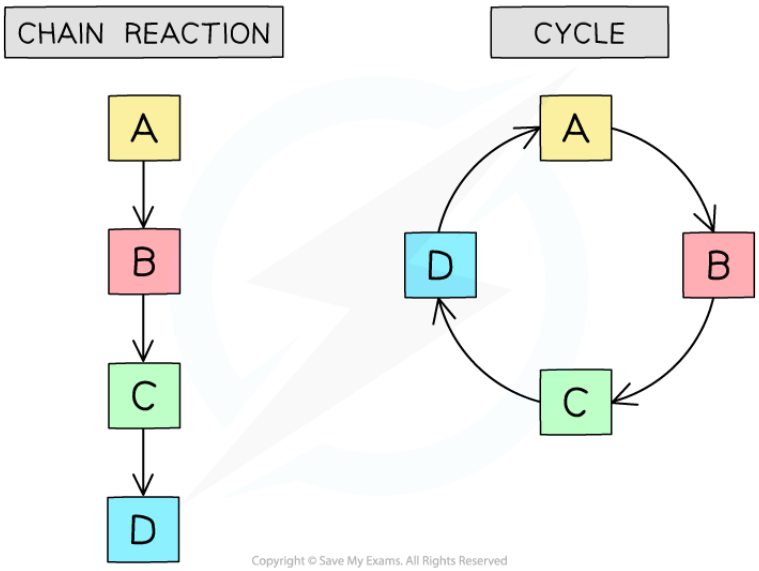
Contents

8.1.1 Metabolic Pathways

Your notes

Metabolic Pathways

- Metabolic pathways involve a **series of small steps**, each step involves a **chemical change**
- The **enzyme-catalysed** reactions that make up metabolic pathways usually consist of **chains** or **cycles**:
  - Chain reactions are a linear sequence with a distinct beginning and end
    - Glycolysis, part of respiration, is an example of a reaction chain metabolic pathway
  - Cycles involve the end product starting the next cycle, these are less common than chain reactions
    - The Calvin cycle, part of photosynthesis, is an example of a cyclic metabolic pathway



A chain metabolic pathway has a distinct start and finish, whereas in a cycle the end product feeds back into the starting reactant

- Chemicals involved in metabolic pathways are called **metabolites** or **intermediates**
  - Some form new molecules within cells
  - Others breakdown molecules and involve an energy transfer

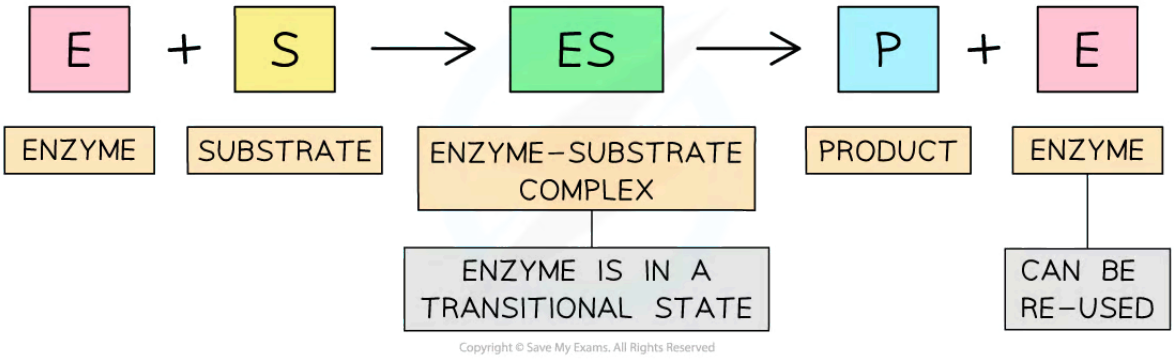
Enzymes & Activation Energy

Your notes

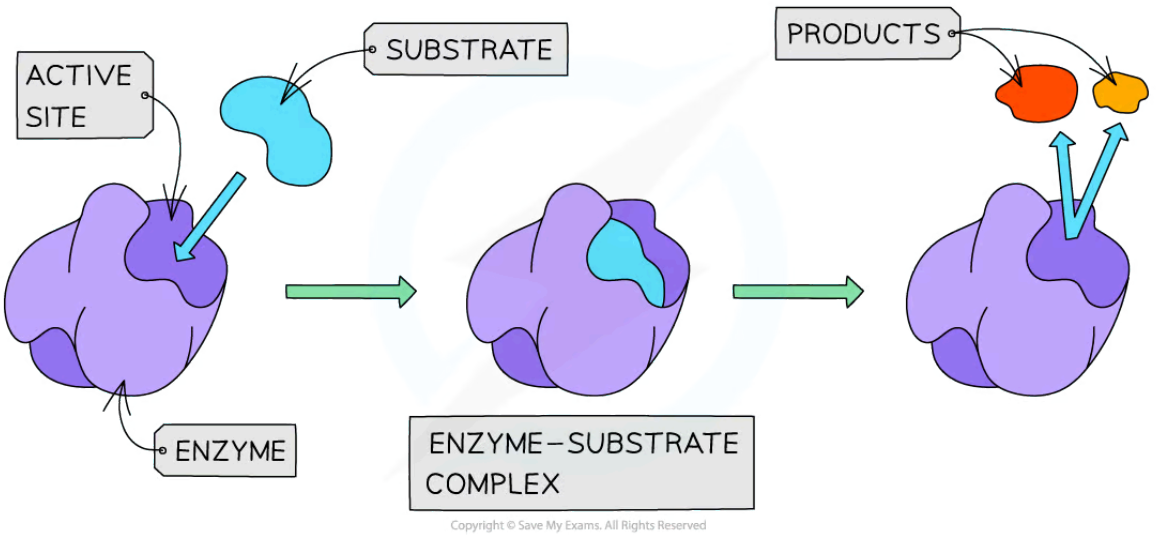
- **Metabolic pathways** are controlled by **enzymes** in a biochemical cascade of reactions
  - Virtually every metabolic reaction within living organisms is catalysed by an enzyme
  - Enzymes are therefore essential for life to exist
- Enzymes are **biological catalysts**
  - 'Biological' because they function in **living systems**
  - 'Catalysts' because they **speed up** the rate of chemical reactions without being used up or undergoing permanent change

The Enzyme-Substrate Complex

- The starting point of a metabolic pathway is a **substrate** which is converted to an end product
- The enzyme works by binding to the substrate at a special site on the enzyme called the **active site**
  - The active site of an enzyme has a specific shape to fit a specific substrate
- Substrates **collide** with the enzyme's active site and this must happen at the **correct orientation** and speed in order for a reaction to occur
- An **enzyme-substrate complex** is formed, temporarily, when the substrate binds to the active site
  - The substrate is said to be in a **transitional state** at this moment
- The product is formed and enzyme is released to take part in another reaction
- The reaction can be shortened to a simple equation



The simple equation can show how an enzyme reaction proceeds



The formation of the enzyme-substrate complex where the substrate is said to be in a transitional state, before forming the product(s)

Enzymes and the lowering of activation energy

- All chemical reactions, including metabolic pathways, are associated with **energy changes**
- Energy may either be released or absorbed during a reaction
  - If energy is released to the surroundings it is an **exergonic** reaction
  - If energy is absorbed from the surroundings it is an **endergonic** reaction
- For a reaction to proceed there must be enough **activation energy**
- Activation energy is the amount of **energy** needed by the substrate to become **unstable** enough for a reaction to occur and for **new products** to be formed
- Enzymes **speed up** chemical reactions because they reduce the **stability of bonds** in the substrate
- Enzymes **lower the activation energy** needed to catalyse a reaction
  - The energy released is unchanged but the activation energy required is lowered
  - The rate of reaction is therefore quicker

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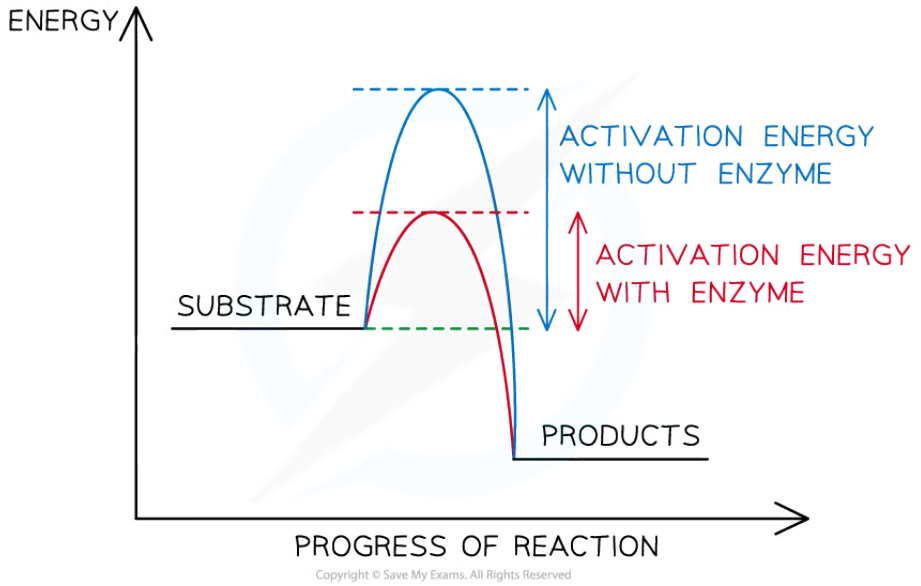

The graph shows how an enzyme lowers the activation energy required for a reaction

Examiner Tip

Don't forget that enzymes are **proteins**, meaning that anything that could **denature** a protein and make it non-operational (such as extremes of heat, temperature, pH etc.) would also denature an enzyme.

Endergonic and **exergonic** reactions are defined by the net the intake or output of energy (respectively) this differs from endo**thermic** and exo**thermic** reactions which are defined by the intake or output of **thermal energy** only.

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8.1.2 Inhibition


Your notes

Enzyme Inhibitors

- **Inhibitors** are chemical substances that can bind to an enzyme and **reduce its activity**
- Inhibitors can be formed from **within the cell** or can be introduced from the **external environment**
- An enzyme's activity can be **reduced** or **stopped,** temporarily, by an inhibitor
- There are two types of inhibitors: **competitive** and **non-competitive**

Competitive inhibitors

- Competitive inhibitors have a **similar shape** to that of the substrate molecules
- They **bind to the active site** of the enzyme, interfering with it and **competing** with the substrate for the active site
- The substrate, therefore, cannot bind to the active site if a competitive inhibitor is already bound

Non-competitive inhibitors

- Non-competitive inhibitors bind to the enzyme at an **alternative site**, which **alters the shape** of the **active site**
- This therefore prevents the substrate from binding to the active site

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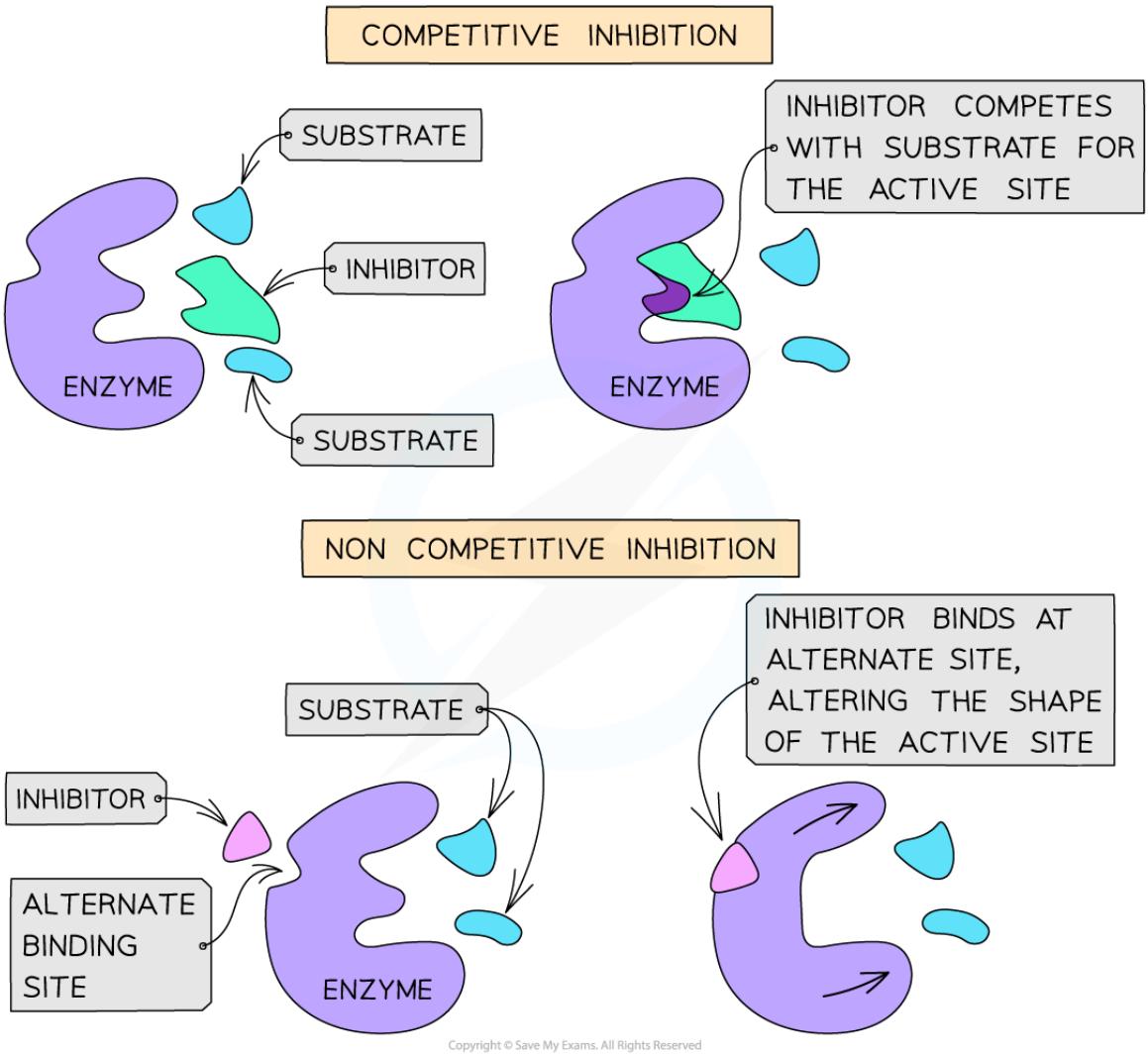

Competitive and non-competitive inhibition

Examples of competitive and non-competitive inhibitors

- An example of a **competitive** inhibitor involves the **enzyme RuBisCo**, an important carbon fixation enzyme in **photosynthesis**
  - **Oxygen** is a competitive inhibitor to this enzyme and blocks the active site for carbon dioxide
  - Therefore carbon dioxide cannot bind to RuBisCo and reactions involved in **photosynthesis slow down or cease to occur**
  - This can be **fatal** to the plant
- An example of a **non-competitive** inhibitor involves the enzyme **cytochrome c oxidase**, a mitochondrial enzyme that catalyses one of the key reactions in aerobic respiration

- **Cyanide ions** are a non-competitive inhibitor that binds to a site on the enzyme and **change the shape of the active site**
- Therefore cytochrome c oxidase cannot carry out its functions in respiration
- This can be **fatal** as it takes too long to produce new enzymes and the organism will die before this can occur
- Cyanide is known as a **metabolic poison** because it interferes with metabolic pathways

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Table comparing competitive and non-competitive inhibitors

Competitive Inhibitors	Non-Competitive Inhibitors
Bind to the active site	Bind to alternative site on the enzyme
Chemically resemble the substrate	Chemically unlike the substrate
Block the active site	Change the shape of the active site
Low concentration allows high substrate concentration to overcome inhibitors	Low concentration doesn't allow high substrate concentration to overcome inhibitors

Examiner Tip

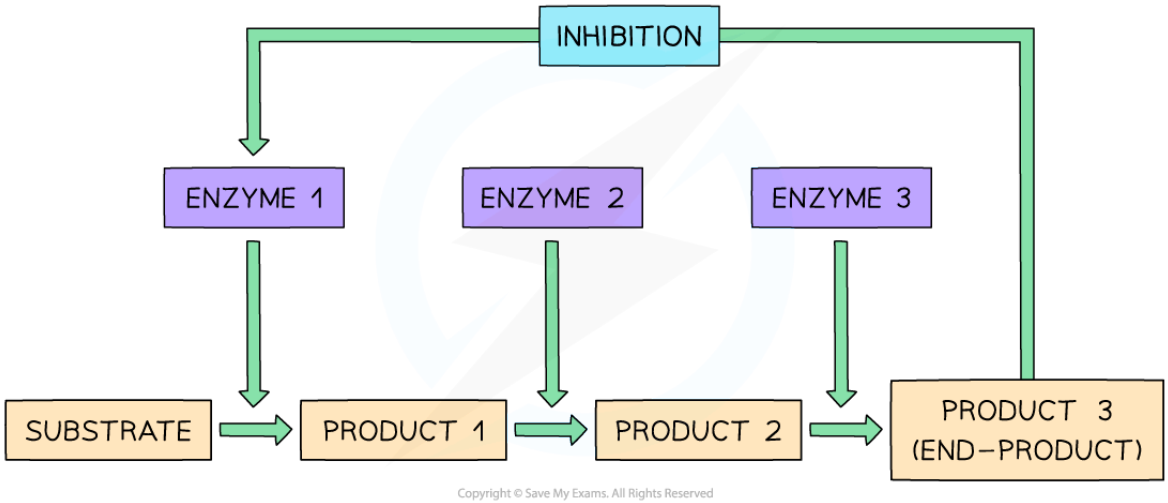
You need to be able to give a named example for competitive and non-competitive inhibition

End-product Inhibition

Your notes

- Enzymes can be **regulated** by chemical substances that bind to a site on the enzyme away from the active site, known as the **allosteric site**
- Binding to this site, away from the active site forms an **allosteric interaction** leading to a reversible change in the **shape and activity**
- Chemicals that regulate the metabolic pathway like this are termed **allosteric regulators**

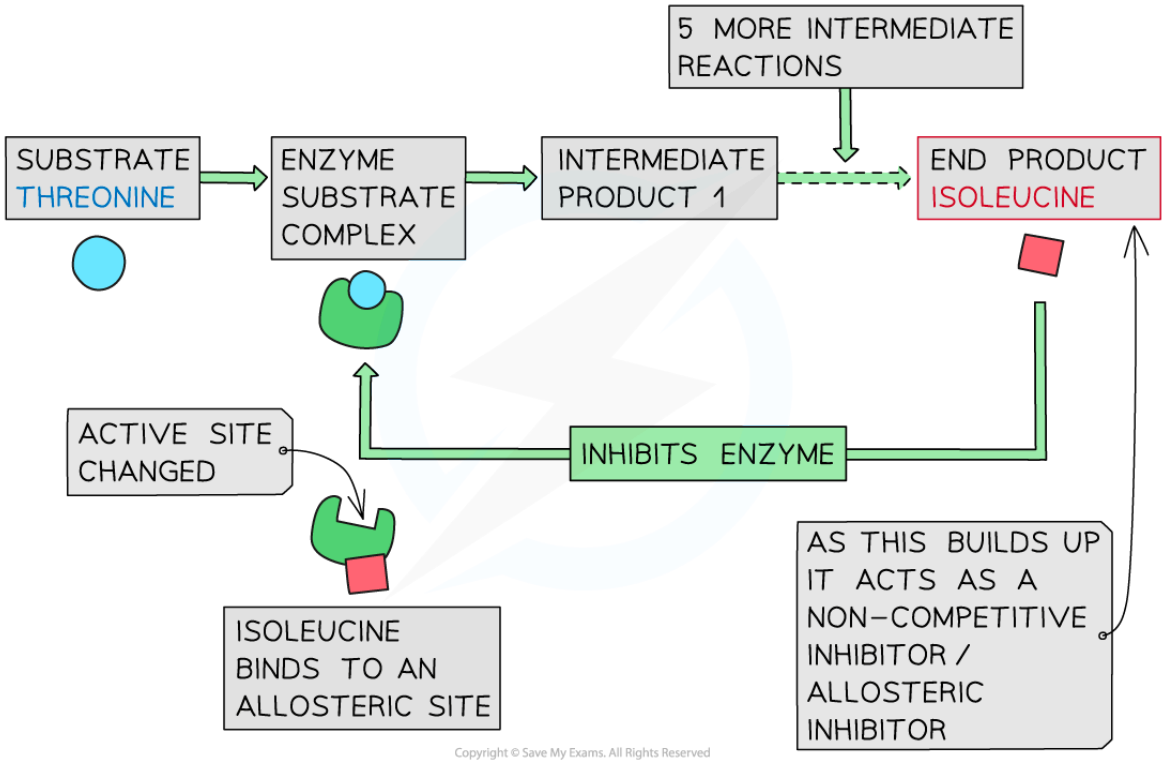
- **End-product inhibition** occurs when the end product from a reaction is present in excess and itself acts as a **non-competitive inhibitor** of the enzyme
- The end product binds to an **allosteric site** on the enzyme and causes inhibition of the pathway, so they are referred to as **allosteric inhibitors**
- Allosteric inhibitors are important to prevent the build-up of **intermediate products** in a metabolic pathway, as each small step of the pathway may produce a new product
- The product therefore does not accumulate and the pathway can continue
  - An outline of the process is as follows:
    - As the enzyme converts substrate to an end product, the process is itself slowed down as the **end-product** of the reaction chain binds to an allosteric site on the original enzyme, changing the shape of the active site and preventing the formation of further **enzyme-substrate complexes**
    - The inhibition of the enzyme means that product levels fall, at which point the enzyme begins catalysing the reaction once again; this is a continuous **feedback loop**
      - The end-product inhibitor eventually detaches from the enzyme to be used elsewhere; this is what allows the active site to **reform** and the enzyme to return to an **active state**



End-product inhibition where the end-product of an enzyme controlled pathway inhibits the starting enzyme and limits the reactions

Worked example

Show, with a **diagram**, the end-product inhibition of the pathway that converts **threonine** to **isoleucine**



Example of end-product inhibition between threonine and isoleucine

Examiner Tip

You need to know the specific example of end-product inhibition of **theonine** and **isoleucine**

Your notes

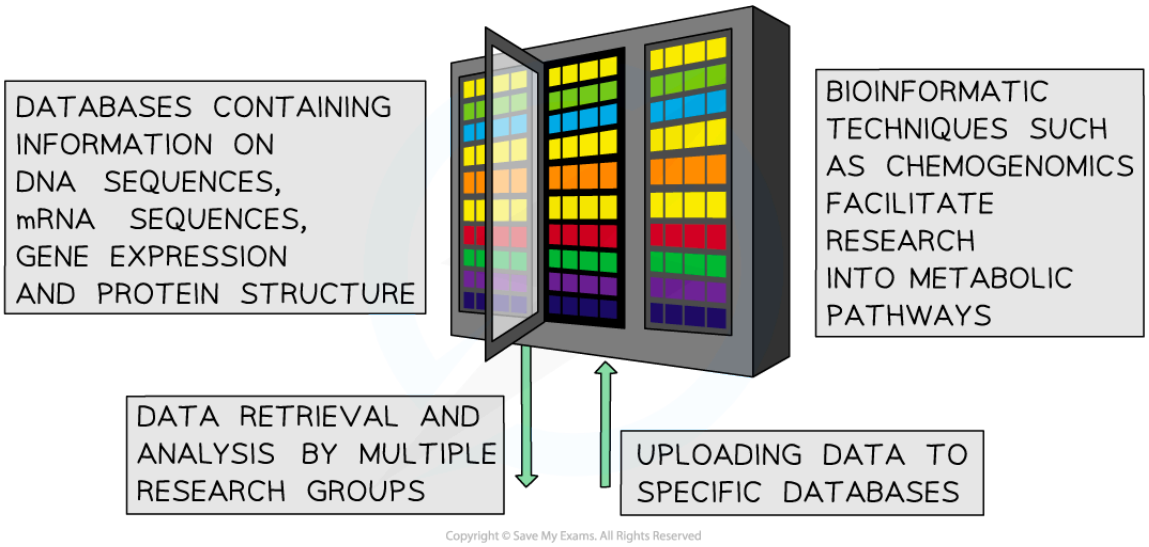
8.1.3 Bioinformatics & Metabolism

Your notes

Bioinformatics: Investigating Metabolism

NOS: Developments in scientific research follow improvements in computing: developments in bioinformatics, such as the interrogation of databases, have facilitated research into metabolic pathways

- **Bioinformatics** is the use of **computers to analyse and sequence data** in biological research
- It has led to the creation of massive **databases** of information on molecules such as proteins, genes and DNA sequences
- Bioinformatics involves multiple scientific research groups contributing into central databases; other groups can then analyse the research and raise queries
- There are a number of different applications of bioinformatics
  - **Testing commercially available drugs** on diseases that the drugs have not been originally targeted for
  - Theoretical molecular chemicals can be developed to **screen databases for new compounds** with the potential for targeting specific diseases, such as malaria
  - **Gene function** can be studied using model organisms with similar sequences
  - When **developing new drugs** scientists can test whole libraries of chemicals individually on a range of model organisms



The use of bioinformatics by scientists

- One bioinformatics technique has specifically facilitated research in **metabolic pathways** and is called **chemogenomics**

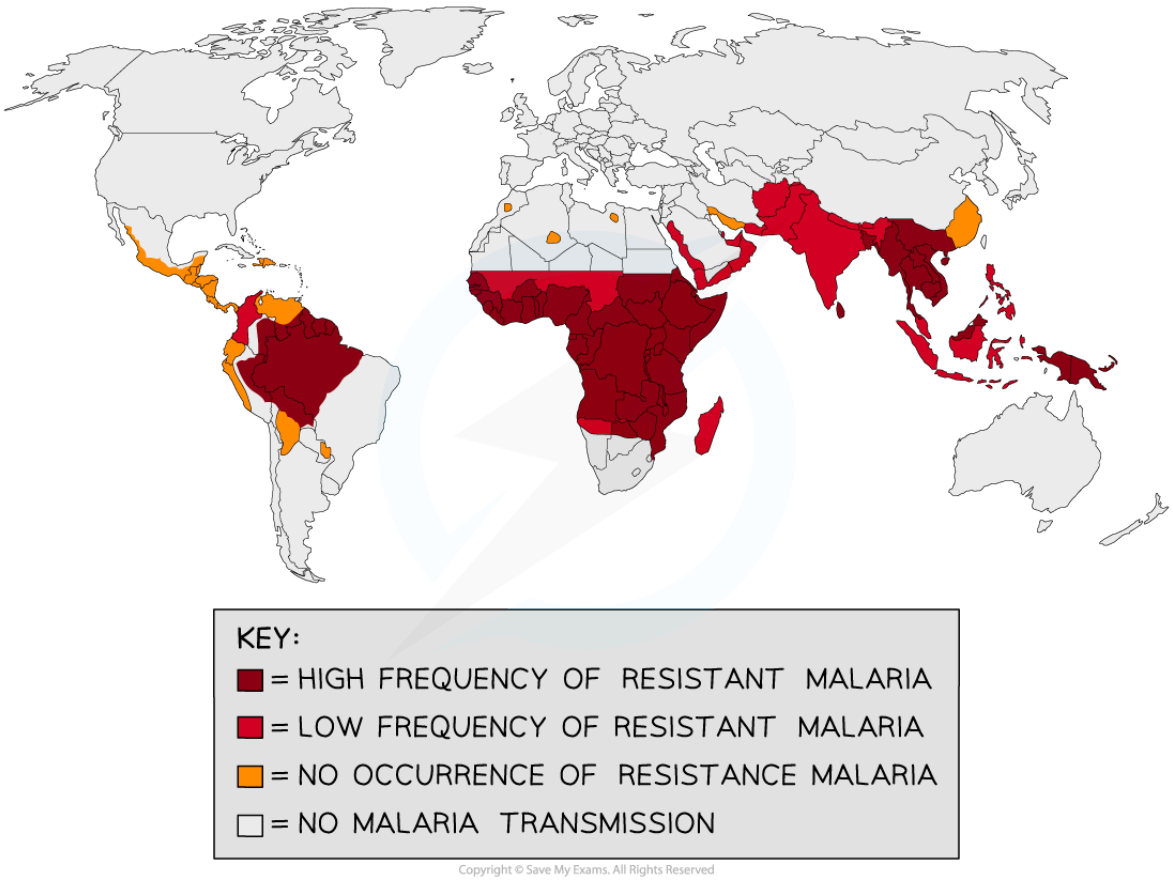
- Chemogenomics focuses on finding chemicals that target enzyme binding sites in order to alter metabolic pathways


Your notes

Bioinformatics: Identifying Anti-malarial Drugs

Your notes

- **Malaria** is a disease caused by the parasitic **protozoans** of the genus ***Plasmodium***
- Some *Plasmodium* protozoa have become **resistant** to many of the available drugs currently used to treat the disease, such as chloroquine
- The development and life cycle of the parasite is governed by specific **enzymes** and **metabolic pathways**
- A global research effort is in place to determine **new methods of treatment** for malaria
- The use of **bioinformatics** has a crucial place in this research by targeting the enzymes and metabolites within the parasite



Map showing the occurrence of resistant malaria parasites across the globe

The use of bioinformatics in identifying malarial inhibitors

- Scientists have sequenced the proteome of the parasitic *Plasmodium falciparum*
- Consequently the enzymes involved in the parasite's metabolism have been **identified** and can be **targeted** for **inhibition**

- Targeting these enzymes and metabolic pathways by inhibition can facilitate the development of **new anti-malarial drugs and medications**
- Bioinformatics can be used to **screen** the parasite's enzymes against a **database of chemicals** to identify potential **enzyme inhibitors**
  - Molecular models of the target enzymes can be **tested against computer designed models of inhibitors**
  - So far over 300,000 chemicals have been screened against resistant malaria strains to identify **19 new chemicals** that can inhibit the parasite's enzymes


Your notes

The use of bioinformatics in finding treatments for malaria

- Aside from targeting malarial inhibitors, bioinformatics has also played a key role developing other **new treatments** for malaria, including
  - Chemical **modification of current anti-malarial drugs** to create hybrid drugs
  - Screening databases for **new compounds** with potential anti-malarial activity
  - **15 new chemicals** have been identified that bind to 61 malarial proteins creating new lines of investigation for scientists to follow in the search for anti-malarials

8.1.4 Skills: Rates of Reaction & Types of Inhibition

Your notes

Calculating & Plotting Rates of Reaction

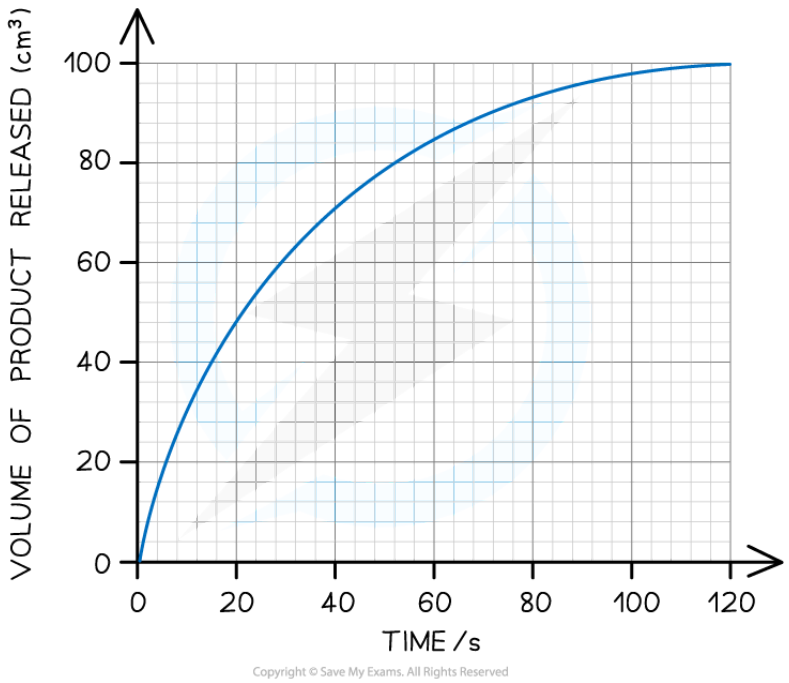
- Enzyme catalysed reactions can be affected by changes in **pH, temperature or substrate concentration**
- The **rate of reaction** can be determined by measuring the **rate of disappearance of a substrate** or the **rate of product accumulated** in a **given time period**
- This may be shown as a change in quantity (usually volume or mass) of substrate or product over a measured time period:

$$\text{RATE OF A REACTION} = \frac{\text{CHANGE IN AMOUNT OF REACTANTS OR PRODUCTS (mol dm}^{-3}\text{)}}{\text{TIME (s)}}$$

- **Or,** if we cannot collect quantitative data on the amount of substrate or product, we can calculate the rate of reaction **based on the time measured** using the following equation:

$$\text{RATE OF REACTION} = \frac{1}{\text{TIME TAKEN (s}^{-1}\text{)}}$$

  - **1 ÷ time taken (seconds)** and should include the units s^{-1}
- A **high** rate of reaction is when the reaction happens in **less time** i.e. it is faster
- A **low** rate of reaction is when the reaction happens in **more time** i.e. it is slower
- The rate of a reaction is likely to change throughout a reaction as the **substrate concentration will decrease** as the reaction proceeds
  - This leads to a graph that starts out as a **directly proportional** straight line (the value on the X increases at the same rate as the value on the Y) but then **plateaus as the reaction slows down**
- The **steeper the line the faster the rate of reaction**
- The rate of reaction can be calculated from a graph plotted where the reaction **time** is shown on the X-axis and the **quantity of product or substrate** is shown on the Y-axis



Graph produced when plotting the volume of a product produced against time

- The gradient is calculated from a point on the graph and used as a measure of the rate of reaction at that point in time
- A **tangent** must be drawn to calculate the change in x and y so the rate of reaction can be calculated
  - E.g. if calculating the initial rate of reaction
    - Place a ruler on the point of **origin** and draw a line that corresponds to the curve during the early part of the reaction
    - **Extend the line** as far as is convenient to perform the calculations e.g. to 60 seconds

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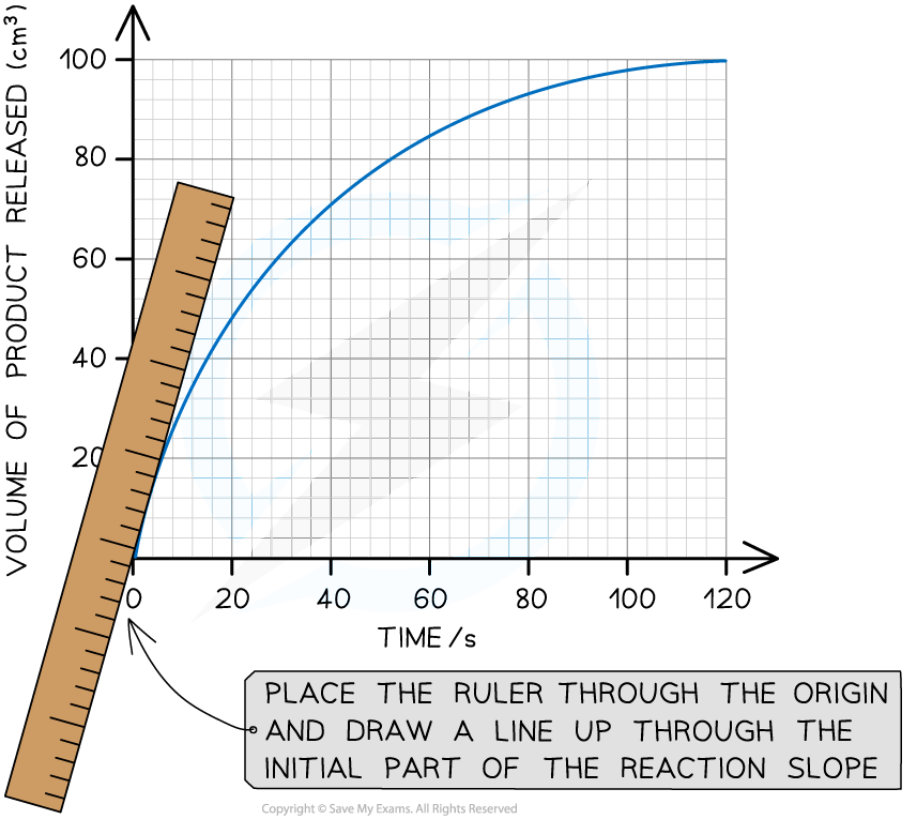


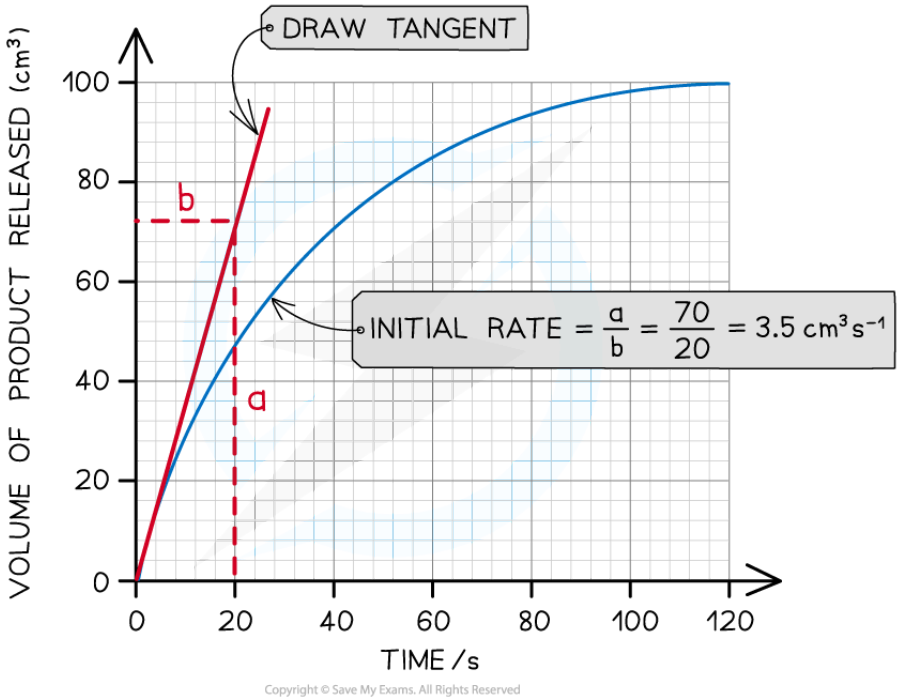
Drawing a tangent to the graph to calculate the initial rate of reaction

Calculating the rate of reaction

- Once the tangent is drawn you can calculate the **gradient** of the line which is equal to the rate of the reaction
  - Initial rate = a ÷ b
  - Where
    - a = change in volume and
    - b = change in time
  - The units will be **cm^3 sec^{-1}** (this means volume per sec)

Your notes

Your notes



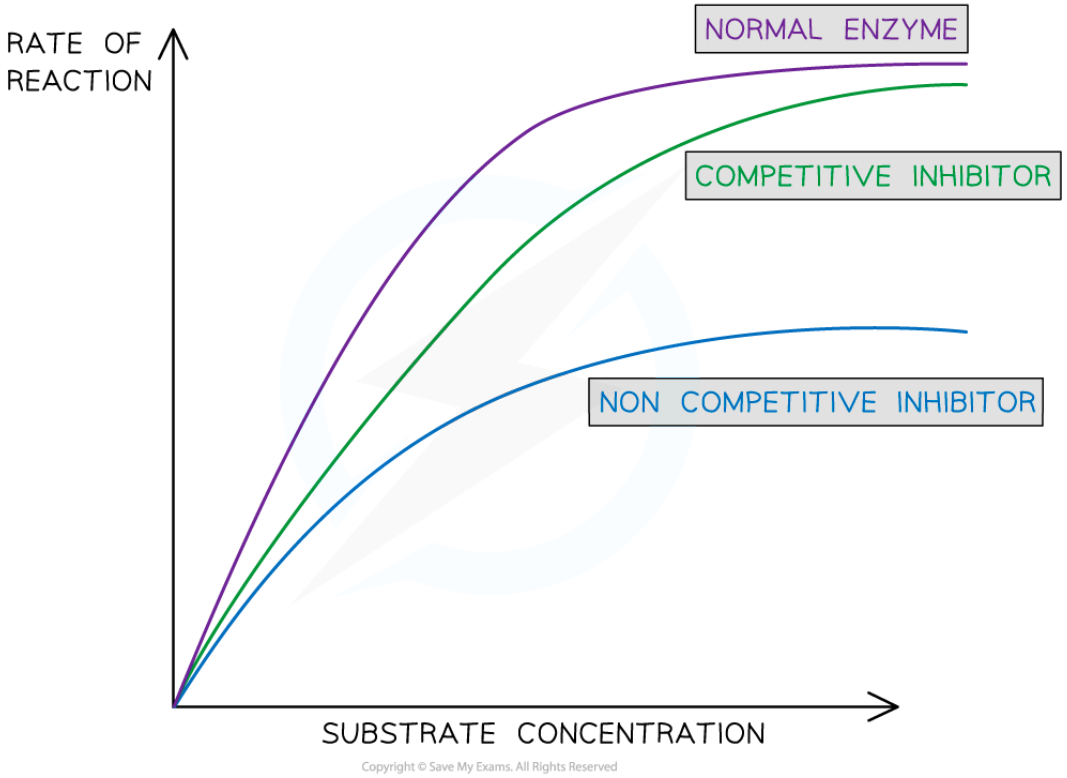
Calculating the rate of reaction from the tangent

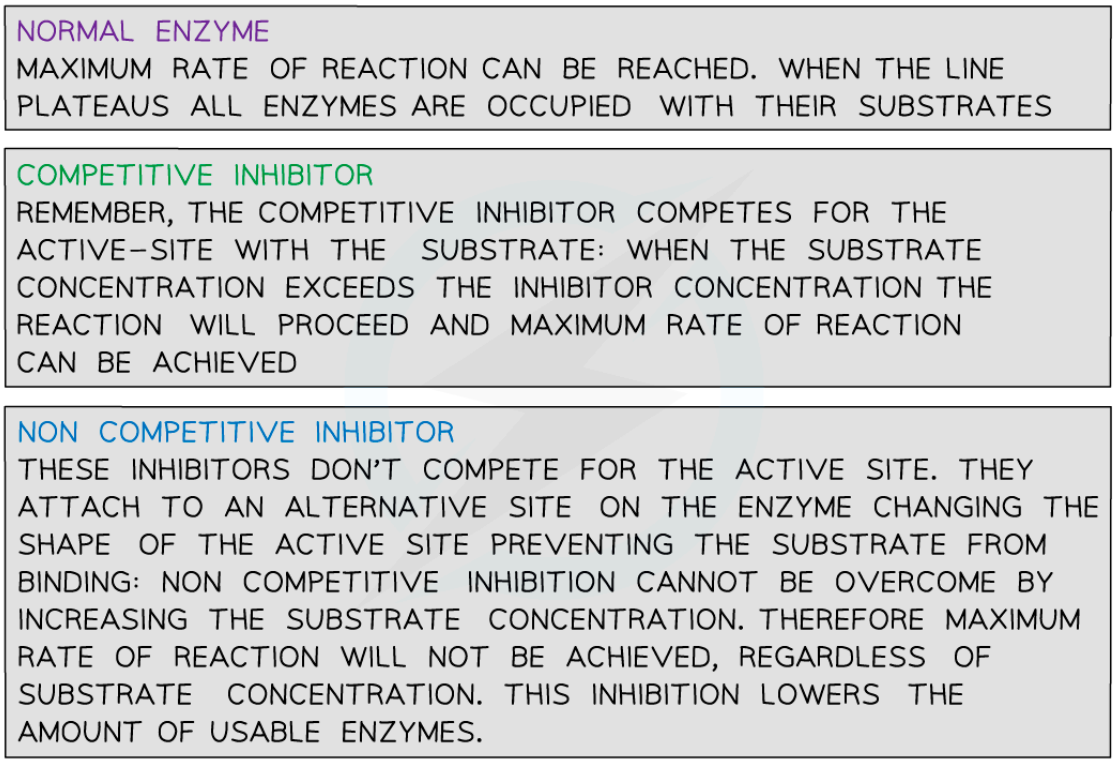
Identifying Types of Inhibition

Your notes

- The effect of competitive and non-competitive inhibitors on enzyme controlled reactions can be represented graphically
- Both types of inhibitors **slow down** or **stop** enzyme activity, decreasing the rate of reaction
- **Increasing** the **concentration** of an inhibitor **reduces** the rate of reaction and eventually, if inhibitor concentration continues to be increased, the reaction will **stop completely**
  - For **competitive inhibitors** countering the increase in inhibitor concentration, by increasing the substrate concentration, **can increase** the rate of reaction but the substrate needs to reach a high enough concentration in order to displace the inhibitor (more substrate molecules mean they are more likely to collide with enzymes and form enzyme-substrate complexes)
  - For **non-competitive inhibitors** increasing the substrate concentration **cannot increase** the rate of reaction, as the shape of the active site of the enzyme remains changed and enzyme-substrate complexes are still unable to form

- A graph can be used to distinguish between the two different types of inhibitors and their effect on the rate of reaction
- The patterns shown are **notably different for each type of inhibitor** and also for an **uninhibited enzyme**





Graph showing different types of inhibitors and their effect on rate of reaction

- A competitive inhibitor will lower the initial rate of reaction (by occupying some of the available active sites), whilst the maximal rate is not affected
  - **Eventually,** the same amount of product will be produced as would have been produced without the competitive inhibitor
- Non-competitive inhibitors lower the initial rate of reaction **and the maximal** rate of reaction
  - A lower amount of product is produced than would normally be produced

Your notes