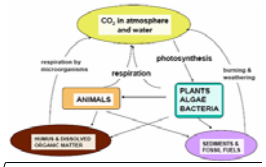
General Principles of Metabolism

Introduction

- Living organisms require energy for three major purposes
  - The performance of **mechanical work** in **muscle contraction** and **cellular movement**
  - The **active transport** of ions and molecules
  - The **biosynthesis** of **macromolecules** from **precursors**
- The **free energy** using in these process maintains them far from equilibrium
- Two kinds of organisms
  - **Phototorophs** get their energy by trapping sunlight
  - **Chemotrophs** get their energy by oxidising foodstuffs generated by phototrophs
- **Metabolism** is a **linked series of chemical reactions**
  - **Catabolic** reactions **convert energy** from **fuels** into **biologically useful forms**
  - **Anabolic pathways require energy**
  - Some are either, called **amphibolic pathways**



Metabolic strategies

Source of carbon		Organic compounds (Heterotrophs)	CO_2 (Autotrophs)
Energy source	Light	Photo-organotrophs (eg: nonsulphur purple bacteria)	Photolithotrophs (eg: plants, algae, bacteria)
	Organic compounds	Chemoorganotrophs (eg: animals, fungi, bacteria)	
	Inorganic compounds		Chemolithotrophs

- **Chemolitotrophs** are able to live in **very hostile conditions** and are believed to be some of the **first organisms** to have lived on earth
- They **oxidise inorganic compounds** to obtain energy
  - **Nitrifying bacteria**
    - $NH3 + 1/2\ O2 + H2O \rightarrow NO2- + 5H+ + 4e-$
    - $NO2- + H2O \rightarrow NO3- + 2H+ + 2e-$
    - The electrons can then be used for oxidative phosphorylation
    - This is the main reason most nitrogen on earth exists as nitrates
  - **Sulphur oxidising bacteria**
    - Use energy from oxdiation of H2S, elemental sulphur and S2O3 2-
    - For example, **thiobacillus concretivorous** - corrodes concrete
    - $S2O3\ 2- + 2O2 + H2O \rightarrow 2SO4\ 2- + 2H+ + 2e-$
    - $S + H2O + 1.5\ O2 \rightarrow SO4\ 2- + 2H+$
  - **Hydrogen bacteria**
    - Gain energy from oxidising H2 gas with N A D+ using the hydrogenase enzyme
    - $H2 + AND+ \rightarrow NADH + H+$

Thermodynamics

- **Eduard Buchner** showed that the same laws of thermodynamics governed cells than everything else - using **yeast juice**
- The **entropy** of the universe must **increase**
  - $\Delta S_{tot} = \Delta S_{system} - \frac{\Delta H_{system}}{T}$ Taking both 1st and 2nd law into account
  - $\Delta G = \Delta H_{system} - T\Delta S_{system}$ **Gibbs Free Energy**
  - To be **exergonic**, a reaction must have this smaller than 0
- Tells us nothing about the rate
- **Free energy** is a **state function** - it depends not on the path taken from reactants to products
- $\Delta G = \Delta G^{\circ\prime} + RT \ln \frac{\prod [\text{Products}]}{\prod [\text{Reactants}]}$
- The **stard-free-energy change** in **biology calculations** is taken at pH 7, at RTP
  - Activities of H+ and H2O are therefore always 0
- At **equilibrium**, we can find a value for the equilibrium constant
- **Overall** free energy change is **additive** (since we have a path function) - therefore, **unfavourable** reactions can be **coupled** to **favourable ones**
  - Shared intermediate
  - Enzyme

- **ATP** is the **universal currency of free energy** in the cell
  - Notes
    - Active form usually a complex with Mg2+ or Mn2+
    - P-O-P bonds are **phosphoanhydride**
    - **Nucleoside diphosphate kinases** catalyse the transfer from different nucleotide triphosphates
  - **High phosphoryl transfer potential**
    - **ADP** and particularly ***Pi*** has much greater **resonance stabilisation** than ATP
    - At **pH 7**, the **triphosphate part** has **four negative charges** - these repell each other
    - **Water** can **bind** *more effectively* to **ADP** and ***Pi*** than to ATP
  - Free energy of hydration is -50 kJ/mol under cellular conditions (standard charge -30.5 kJ/mol)
  - Phosphoryl transfer potential is intermediate
    - Some (phosphoenolpyruvate, 1,3-bisphosphoglycerate, creatine phosphate) have higher phosphoryl transfer potential
    - Others have less
    - This makes it an **ideal carrier of phosphoryl groups**
    - **Phosphocreatine**
      - Under high energy demans or metabolic crises acts as a "**reservoir**" of high-energy phosphates
      - Buffers ATP
      - Can be measured using 31P NMR spec

Reduction and Oxidation

- **REDUCTION** is the **GAIN OF ELECTRONS** [sometimes gain of hydrogen]
- **OXIDATION** is the **LOSS OF ELECTRONS** [sometimes loss of hydrogen]

Regulation of metabolism

- Controlling the amount of enzymes
- Controlling catalytic activity
  - Reverse allosteric control
    - First step in the cycle is inhibited by the product
    - Can be almost instantaneous
  - Reversible covalent modification
    - Glycogen phosphorylase (glycogen --> glucose pathway) is activated by the phosphorylation of a serine residue when glucose is sparse
  - Homones coordinate metabolic relations between different tissues (often by regulating reversible modification of key enzymes)
  - The **energy charge** of a cell is
    - [ATP] + 1/2 [ADP] / [ATP] + [ADP] + [AMP]
    - **Atkinson** showed that **catabolic pathways** are **inhibited** by **high energy charge** and vice versa
    - On a graph of rate vs. energy charge, the graphs are **steep** near an energy charge of about **0.8 - 0.85**
    - Tha graphs for catabolic and metabolic pathways intersect there
    - Clearly, this is designed to buffer energy charge within narrow limits
- controlling the accessibility of substrates
  - Enhanced by compartmentalisation in eukaryotes
  - Can segregate opposed reactions
  - e.g.: fatty acid synthesis and oxidation take place in different parts of the cell (cytoplasm and mitoc respectively)
  - Controlling the **flux** of substrates is also useful - **glucose breakdown** can only occur if **insulin** is present to promote its entry into the cell!

Recurring motifs - activated carriers

- **ATP** is an activated carrier of phosphate groups
- **Activated carriers** for **fuel oxidation**
  - Electrons are not transferred directly to O2 but not **carriers** which are either **pyridine** or **flavin nucleotides**
  - The reduced form of these carriers then transfers electrons to O2
  - **NICOTINAMIDE ADENINE DINUCLEOTIDE** (N A D) is a major electron carrier
    - Active part is a **nicotinamide ring**
    - **Pyridine derivative** synthesised from **niacin**
    - Can accept **one hydrogen ion** and **two electrons**
  - **FLAVIN ADENINE DINUCLEOTIDE** (**FAD**) is another
    - **Active site** is the vitamin **riboflavin**
- **Activated electron carriers for reductive biosythesis**
  - High energy electrons (reducing power) is needed in most biosyntheses
  - Electron carrier is **NADP+** which is **identical** to **N A D+** except that it has an additional phosphate group where N A D only has an H atom
  - Acts as a "**tag**" - allows the cell to establish **two redox potentials**
- **Activated carrier of two-carbon fragments**
  - **Coenzyme A** is an activated carrier of **acetyl groups**
  - These can link to CoA at its **terminal sulfhydril group** by **thioester bonds**
  - Hydrolysis of the thioester bond is exergonic (-31.5 kJ/mol), and so acetyl CoA has a **high acetyl-group transfer potential**
    - More so than an ester
    - Resonance structure formed by C=O with an ester is stronger than in a thioster
- **Biotin** is an **activate carrier of CO2**
- **Uridine diphosphate glucose** is an **activate carrier** for **glucose**

Oxidation of carbon compounds

- Important source of cellular energy
- Energy released is sued to make ATP from ADP and Pi
  - Oxidative phosphorylation
    - Energy converted to ion gradient
    - Used to make ATP
  - Substrate-level phosphorylation
    - Energy trapped as high phosphoryl-transfer potential compounds
    - Used to form ATP
- In **aerobic organisms**, the ultimate electron acceptor is O2 to make CO2
- Steps
  - Large molecules of food are broken down into **smaller units** (no energy released)
  - Numerous small molecules degraded into a few simple units playing a crucial role in metabolism
  - These are used to make ATP (via substrate-level/oxidative phosphorylation)