Energy and life

- Biological systems are powered by oxidation of biomolecules made mainly of C, H and O.
- The food biomolecules are mainly
  - Lipids (fats)
  - Carbohydrates (starch and sugar)
  - Proteins
- All these are broken down by different pathways.
- In this lecture we will focus on the final pathway by which energy is released from all types of food molecules.

Energy

For energy to be useful it has to be available in a controlled manner. Energy in a living system has to have the following features:
- The energy must be released gradually.
- It must be stored in readily accessible form.
- It must be carefully controlled so it is available when needed.
- Just enough energy must be released as heat to maintain body temperature.
- Energy in forms other than heat must be available to drive chemical reactions that are not favorable at body temperature.
When $\Delta G < 0$, the reaction releases energy. When $\Delta G > 0$, the reaction requires energy input. Energy input can come in different forms.

**Molecular Energy Storage**

- Energy from sunlight causes allows a chemical reaction to occur that would not occur otherwise.
- This reaction allows energy to be stored in chemical bonds in the sugar molecule.
- Animals break down sugar and starches in order to use the energy.
- Animals use energy stored in a molecule ATP.

(Breaking bonds in stable molecule requires energy, always. So this language is a bit confusing. Energy is only available because other bonds are formed.)

**Photosynthesis**

- The formation of sugar from CO$_2$ and H$_2$O requires an energy source.
- Breaking down sugar into CO$_2$ and H$_2$O liberates energy.

**Mitochondria**

- A mitochondrion (singular of mitochondria) is part of every cell. Mitochondria are responsible for processing oxygen and converting substances from the foods we eat into energy for essential cell functions.
- Mitochondria produce energy in the form of adenosine triphosphate (ATP), which is used throughout the cell for use in numerous cell functions.
- 90% of the cell’s ATP production takes place in the mitochondria.
The mitochondrion

Cells have many mitochondria. The citric acid cycle takes place in the matrix. Electron transport and ATP production, the final stage in biochemical energy generation, takes place at the inner surface of the inner membrane. The numerous folds in the inner membrane—known as cristae—increase the surface area over which these pathways can take place.

• It is believed that the mitochondria were free living bacteria that got trapped in the cell.
• The mitochondria contain its own DNA and can synthesize protein
• The mitochondria have a symbiotic relationship with the cell.
• All mitochondria in the cell genetically come from the mother.
• The parts of the body that require a larger amount of energy have a larger number of mitochondria.

An Overview of Metabolism and Energy:

• All the chemical reactions that take place in an organism together constitute its metabolism.
• Metabolic pathways can be linear, cyclic or spiral.
• The citric acid cycle is cyclic and electron transport is linear.
• In linear metabolism different enzymes are used, and the product of one reaction is the substrate for the next.
• In cyclic metabolism a series reactions regerates one of the initial reactants.
• In a spiral metabolism, the same enzyme progressively builds up or breaks down a molecule.

Pathways for the digestion of food and the production of biochemical energy.

• Step 1 Digestion
• Step 2 Acetyl–S Co A Production:
The small molecules from the digestion follow separate pathways that move the carbon atom into two carbon acetyl groups. The acetyl groups are attached to coenzyme A by a bond between the sulfur atom of the thiol (–SH) group at the end of coenzyme A and the carbonyl atom of the acetyl group. Acetyl–S Co A is an intermediate in all classes of food molecules. It carries the acetyl group into the common pathway of catabolism—the citric acid cycle and stage 4, electron transport and ATP production.

Catabolism and Anabolism

• Metabolic reaction pathways can either be catabolic or anabolic. Catabolic pathways break down molecules and release energy. Anabolic pathways build larger molecules from smaller pieces and require energy.
Step 3: Citric acid cycle
Within the mitochondria the acetyl group carbon atoms are oxidized to the CO$_2$ that we exhale. Most of the energy released in the oxidation leaves the citric acid cycle in the chemical bonds of reduced coenzymes (NADH, FADH$_2$). Some energy also leaves the cycle stored in the chemical bonds of ATP or a related triphosphate.

Stage 4: ATP production
Electrons from the reduced coenzyme are passed from molecule to molecule down the electron transport chain. Along the way, their energy is harnessed to produce more ATP. At the end of the process these electrons, along with the hydrogen ions from the reduced coenzymes combine with the oxygen we breath to produce water.

ATP and Energy Transfer

ATP is hydrolyzed to give a phosphate group and ADP with release of energy

$$\text{ATP} + \text{H}_2\text{O} \rightarrow \text{ADP} + \text{PP}_\text{i} + \text{H}^+ \quad \Delta G = -7.3 \text{kcal/mol}$$

The reverse of ATP hydrolysis is a phosphorylation reaction

$$\text{ADP} + \text{PP}_\text{i} + \text{H}^+ \rightarrow \text{ATP} + \text{H}_2\text{O} \quad \Delta G = +7.3 \text{kcal/mol}$$

Production, transport and use of biochemical energy all require the ADP/ATP inter conversion.
ATP - the “HIGH ENERGY molecule”

ATP is reactive and a useful amount of energy is released when a phosphoryl group is released from it by hydrolysis.

If ATP generated a very high amount of energy then it will be very difficult to regenerate the molecule.

### Table: Free Energies of Hydrolysis of Some Phosphates

<table>
<thead>
<tr>
<th>Compound Name</th>
<th>Function</th>
<th>ΔG (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>oxaloacetate</td>
<td>Other intermediate in conversion of glucose</td>
<td>-11.2</td>
</tr>
<tr>
<td></td>
<td>to pyruvate (by glycolysis) — stage 4, Figure 21.0</td>
<td></td>
</tr>
<tr>
<td>ATP</td>
<td>Principal energy carrier</td>
<td>7.3</td>
</tr>
<tr>
<td>inorganic phosphate</td>
<td>Energy storage in muscle cells</td>
<td>10.3</td>
</tr>
<tr>
<td>inorganic phosphate</td>
<td>First intermediate in breakdown of carbohydrates stored as starch or glycogen</td>
<td>-5.0</td>
</tr>
<tr>
<td>inorganic phosphate</td>
<td>First intermediate in glycolysis</td>
<td>-3.3</td>
</tr>
<tr>
<td>inorganic phosphate</td>
<td>Second intermediate in glycolysis</td>
<td>3.3</td>
</tr>
</tbody>
</table>

ATP is reactive and a useful amount of energy is released when a phosphoryl group is released from it by hydrolysis.

If ATP generated a very high amount of energy then it will be very difficult to regenerate the molecule.
ATP hydrolyses at a very slow rate in the absence of catalyst, causing the stored energy to be released only in the presence of appropriate enzyme.

- Catabolism releases the energy bit by bit as and when required.
- In a series of reactions the overall energy change is equal to the sum of the energy changes of individual steps.
- In the body many reactions take place that are not favorable. For such reactions to take place energy is supplied from the ATP reaction hydrolysis.

An example of such a reaction is the phosphorylation of glucose. This is the first step in the metabolic use of glucose.

\[
\begin{align*}
\text{Glucose} + 6\text{HPO}_4^{2-} & \rightarrow \text{Glucose}6\text{-phosphate} + 6\text{H}_2\text{O} & \Delta G = 3.3\text{kcal/mol} \\
\text{ATP} + \text{H}_2\text{O} & \rightarrow \text{ADP} + 6\text{HOPO}_4^{2-} + \text{H}^+ & \Delta G = -7.3\text{kcal/mol} \\
\text{Glucose} + \text{ATP} & \rightarrow \text{Glucose}6\text{-phosphate} + \text{ADP} & \Delta G = -4.0\text{kcal/mol}
\end{align*}
\]
Such coupled reactions do not take place separately in two steps as written above. The net change occurs all at once as represented by the overall reaction. No intermediate HOPO$_4^{2-}$ is formed and the phosphoryl group is transferred directly from ATP to glucose.

The extra energy released in the above reaction is utilized to increase the body temperature. There are other such reactions in the biological system.

Strategies of Metabolism

- Catabolism releases the energy bit by bit as and when required.
- In a series of reactions the overall energy change is equal to the sum of the energy changes of individual steps.
- In the body many reactions take place that are not favorable. For such reactions to take place energy is supplied from the ATP reaction hydrolysis.

Oxidized and reduced coenzymes:

Many metabolic reactions are oxidation reduction reactions. Food molecules are oxidized to release energy.

To keep the supply of the oxidizing and reducing agents many coenzymes continuously keep cycling between their oxidized and reduced forms in the same manner as the ATP –ADP cycle.
The coenzymes continuously cycle between oxidized and reduced forms:

The above coenzymes continuously keep cycling between oxidized and reduced forms. They are also referred to as electron carriers.

To review the oxidation and reduction reactions:

- **Oxidation** is the loss of electrons, loss of hydrogen or the addition of oxygen.
- **Reduction** is the gain of electrons, gain of hydrogen or the loss of hydrogen.

When one substance oxidizes another one simultaneously reduces.

- **LEO** the lion goes GER
  - Loss of Electrons is Oxidation
  - Gain of Electrons is Reduction

\[
\text{Fe}^{2+} \rightarrow \text{Fe} \quad \text{(reduction)}
\]
Oxidation Reduction reaction of NAD+ to NADH/H+

The Citric Acid Cycle (Tri Carboxylic Acid Cycle or Kreb’s Cycle)

- The third stage of catabolism is the citric acid cycle.
- The carbon atoms from the first two stages are carried to the third stage as acetyl group bonded to coenzyme A. The acetyl group in the Acetyl-SCoA is easily removed in an energy releasing hydrolysis.

\[ \text{H}_3\text{C} \text{-SCoA} + \text{H}_2\text{O} \rightarrow \text{H}_2\text{C} \text{-CO} + \text{H}^+ + \text{H}^+ \]
\[ \Delta G = -7.5 \text{ kcal/mol} \]

- The eight steps of the cycle produce two molecules of carbon dioxide, four molecules of reduced coenzymes, and one energy-rich phosphate (GTP). The final step regenerates the reactant for step 1 of the next turn of the cycle.
Step 1 & 2

4 carbon oxalo acetate + 2 carbon acetyl group

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrate is a tertiary alcohol so it cannot be oxidized</td>
<td>Isocitrate is a secondary alcohol that can be oxidized to ketone</td>
</tr>
</tbody>
</table>

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Step 3 & 4

- Both steps are oxidations and rely on NAD⁺ as the oxidizing agent (When NAD⁺ acts as an oxidizing agent it must be reduced.)
- One CO₂ leaves at step 3 and the OH of isocitrate is oxidized to a keto group. (A keto group is a group with a C=O, with a carbon atom on either side of the carbon with the double bond to the oxygen. The enzyme is an isocitrate dehydrogenase complex (an oxidoreductase).)
- A second CO₂ leaves the step 4 and the resulting succinyl group is added to coenzyme A. The enzyme for this step is a Ketoglutarate dehydrogenase complex (another oxidoreductase).

- When the body uses energy at a high rate the ADP accumulates and acts as an allosteric activator (the binding of a molecule to one side of the enzyme affecting the binding of another molecule to a different site) for enzymes in step 3.
- When body has enough energy NADH is present in excess and acts as an inhibitor for the enzyme in step 3.
- In both electrons and the energy are transferred in the reduction of NAD⁺.
- The succinyl –SCoA carries 4 carbon atoms to the next step after the loss of 2 carbons as CO₂.
Step 5
- The conversion of succinyl-SCoA to succinate releases free energy. This reaction is coupled with phosphorylation of guanosine diphosphate (GDP) to give GTP.
- GTP is similar to ATP and carries energy.
- In some cells GTP is directly converted to ATP.
- Step 5 is the only step in which generates an energy rich phosphate.
- The enzyme is succinyl CoA synthetase (a ligase).

Step 6
- The succinate is oxidized by removal of 2 H atoms to give fumarate.
- The enzyme for this reaction is part of the inner mitochondrial membrane.
- The reaction also requires the coenzyme FAD which is covalently bound to its enzyme.
- The coenzyme FAD is converted to FADH₂.
- The enzyme is succinate dehydrogenase (an oxidoreductase).

Step 7 & 8
The citric acid cycle is completed by the regeneration of oxaloacetate, a reactant for step 1.
- In step 7 water is added across the double bond of fumarate to give malate.
  The enzyme is fumarase (a lyase).
- In step 8 the oxidation of malate, a secondary alcohol, gives the oxaloacetate.
  The enzyme is malate dehydrogenase (an oxidoreductase).
Net Result of Citric Acid Cycle:

\[ \text{Acetyl – SCoA} + 3\text{NAD}^+ + \text{FAD} + \text{ADP} + \text{HPO}_4^{2-} + \text{H}_2\text{O} \rightarrow \text{HSCoA (coenzyme A)} + 3\text{NADH} / \text{H}^+ + \text{FADH}_2 + \text{ATP} + 2\text{CO}_2 \]

Production of four reduced coenzyme molecules (3 NADH and 1 FADH\(_2\)).
Production of one energy rich molecule (GTP).

- In the Creb’s cycle we produce only one high energy molecule. The reduced coenzymes NADH and FADH\(_2\) are used to create more high energy molecule.
- The high energy molecule produced by reactions involving both of these produce many ATPs.
- This is done using electron transport.

The electron transport chain and ATP production:

- The reduced coenzyme molecules in the Creb’s cycle are ready to transfer their energy to produce more ATP.
- This takes place by a series of oxidation reduction reactions where electrons are passed along to carrier molecules.
- Each reaction in this series is favorable or exergonic.
- These sequences of reactions are known as the electron transport chain or the respiratory chain.
- The enzymes and the coenzymes for these reactions are embedded in the inner membrane of the mitochondrion.

In the last step of the reaction the electrons combine with oxygen and hydrogen ions to produce water.

\[ \text{O}_2 + 2e^- + 4H^+ \rightarrow 2\text{H}_2\text{O} \]

This reaction is fundamentally the combination of hydrogen and oxygen to form water.

Carried out at once this reaction is explosive.

The electrons moving down the electron transport pathway that is nothing but a series of Fe\(^{2+}/Fe\(^{3+}\) or coenzyme Q oxidation reduction cycles. Free energy is released in these reactions. This energy is used to transport the hydrogen ions from the mitochondrial matrix to the mitochondrial intermembrane space that is otherwise impermeable to hydrogen ions.
• This results in a higher concentration of hydrogen ions in the intermembrane space, this process is in contradiction to the natural tendency of ions to be equally distributed. Therefore it requires additional energy.

**Electron Transport:**

• 4 Enzyme complexes embedded in the mitochondrial inner membrane.
• 2 electron carriers that move from one complex to another.

**Enzyme complexes** are large polypeptide complexes and electron acceptors.

The mitochondrial electron-transport chain and ATP synthase.

• The red line shows the path of electrons, and the green lines show the paths of hydrogen ions. The movement of hydrogen ions across the inner membrane creates a higher concentration on the intermembrane side of the inner membrane than on the matrix side. **The energy released by hydrogen ions returning through the membrane (through ATP synthase) provides the energy necessary to make ATP.**
Essential features of the electron-transport pathway:

- Hydrogen and electrons from the NADH and FADH$_2$ enter the electron transport chain at enzyme complexes I and II respectively.
- FADH$_2$ is produced in step 6 of the citric acid cycle and the enzyme required for that step is a part of the above mentioned enzyme complex. FADH$_2$ does not leave the complex once it is produced.
- It is immediately oxidized there by coenzyme Q.
- Electrons are passed from weaker to stronger oxidizing agents, with energy release at each step.

- Hydrogen ions are released for transport through the inner membrane at complexes I, III and IV.
- The hydrogen ion concentration difference creates a potential energy difference across the membrane.
- This potential energy is used for ATP synthesis.

ATP Synthesis:

- ATP synthesis as an oxidative phosphorylation process. The hydrogen ions that are pushed into the mitochondrial intermembrane space return into the matrix through the channel that is a part of the ATP synthase enzyme complex.

- In doing so they release the potential energy they gained. The energy they release drives the phosphorylation of ADP reaction with hydrogen phosphate ion (HOPO$_4^{2-}$).

$$\text{ADP} + \text{HOPO}_4^{2-} \rightarrow \text{ATP} + \text{H}_2\text{O}$$
• 8 electrons are lost from acetyl CoA and stored in FADH$_2$ and NADH.
• These 8 electrons are responsible for about 36 H$^+$ ions.
• These 36 H$^+$ ions flowing through ATP synthase will generate about 9 ATPs.

• So one Crebs cycle will generate 9 ATPs and one GTP

Summary
• Energy is used in organisms in a controlled way.
• This is possible because energy can be stored in high energy molecules such as ATP.
• An ATP equivalent, and the reduced form of the coenzymes NADH and FADH2 are produced during the Citric Acid Cycle.
• The coenzymes produced in the Citric Acid cycle are used in Electron Transport to generate 8 more ATPs
• (Read in your text about harmful substances that can be byproducts of these pathways.)