The chemistry of life is organized into metabolic pathways

- The sum of an organism’s chemical reactions is called **metabolism**.
- A cell’s metabolism is an elaborate road map of the chemical reactions in that cell.
- Metabolic pathways alter molecules in a series of steps.
Metabolic Pathways in Living Things
(each dot is a different molecule)

The inset shows the first two steps in the catabolic pathway that breaks down glucose.

- **Catabolic pathways** release energy by breaking down complex molecules to simpler compounds.
  - This energy is stored in organic molecules until it is needed to do **work** in the cell.

- **Anabolic pathways** use energy to build complicated molecules from simpler compounds.

- **The energy released by catabolic pathways is used to drive/power anabolic pathways.**

- **Enzymes** selectively **speed up** pathways/steps to make all the reactions happen at the right time & at the right rate. They control metabolism.
  - The activity of enzymes is regulated (turned on & off) to maintain an appropriate balance of supply and demand.
Chemical Reactions

- Chemical reactions (rxns) are processes that transform one set of chemicals into another
  - Mass and Energy are conserved during these transformations
  - Forms of energy
    - Potential energy – chemical, mechanical, positional
    - Kinetic energy – movement, heat, light

- **REACTANTS**: the elements or compounds that enter into a chemical rxn
- **PRODUCTS**: the elements or compounds produced by the chemical rxn

Matter & Energy are conserved in chemical reactions

- Example: Burning wax candle

http://commons.wikimedia.org/wiki/File:Candle_icon.png
Relationship between Potential Energy & Stability

- Which ruler has more potential energy?
- Which ruler is more stable?
  - Greater P.E., less stability →
  - Less P.E., more stable

Energy Changes in Chemical Reactions

- Energy-releasing chemical reactions often occur **spontaneously**.
- Energy-consuming reactions will not occur without a constant input or source of energy
Activation Energy

- **Activation Energy** ($E_A$) represents the energy “barrier” to a reaction. It is the energy input needed for a reaction to proceed.
- Even energy-releasing reactions often need an input of energy to get started.

Catalyzed Reactions

- Most metabolic reactions occur too slowly at body temp ($37^\circ$C) to sustain life as we know it.
- Biological systems and organisms rely heavily on organic catalysts, called **enzymes**, to speed up reactions.
  - **Catalyst**: a substance which speeds up a chemical reaction without being consumed or “used up”
  - Enzymes are *highly specific* catalysts, each kind catalyzing only one or just a few reactions
  - Enzymes are **proteins**. (usually)
What do enzymes do?

- Speed up rate of metabolic reactions by lowering the activation energy ($E_a$)
- Lower $E_a$ by stabilizing the transition state of a reaction

Enzyme Specificity

- An enzyme binds to its reactant/s (called its substrates) at its active site.
- The active site is a region on the enzyme that is chemically & geometrically fashioned to fit and attach to the substrate like a custom-made glove.
- An enzyme is specific to one substrate molecule, the way a lock can only be opened by one specifically-shaped key.

Enzymes (E) bind to their substrates (S) through a variety of bonds or interactions such as:
- Hydrogen bonds
- Ionic bonds
- Hydrophobic interactions
- Covalent bonds
Specificity of an Active Site

Unfolded protein

Folded protein (with a functional active site)

Zoomed in view of Active site with Substrate

What kinds of bonds or attractions can be seen between the enz & substrate?

What would happen to the attraction between enz & substrate if the orange, green, and blue R groups were changed from polar (shown) to nonpolar R groups?

Induced Fit

- The initial attachment or binding of the substrate causes the enzyme to change shape slightly to bind even better -- this is called an induced fit.

- The resulting Enzyme-Substrate complex holds the substrate(s) in such a way as to make the reaction more energetically favorable.
Enzymes are Reuseable

• As Products are made they are released from the Enzyme which reverts to its original state, ready to bind another Substrate.

E + S --> E-S --> E + P

Both Dehydration Synthesis & Hydrolysis are Enzyme-Catalyzed Rxns
Naming Enzymes

• Commonly, enzymes are named after the substrate they act upon and/or the type of rxn they catalyze. (but as expected, there are exceptions)

• Most enzyme names end in -ase.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>sucrose</td>
<td>sucrase</td>
</tr>
<tr>
<td>lipid</td>
<td>lipase</td>
</tr>
<tr>
<td>DNA polymer</td>
<td>DNA polymerase</td>
</tr>
<tr>
<td>lactose</td>
<td>lactase</td>
</tr>
<tr>
<td>succinate</td>
<td>succinate dehydrogenase</td>
</tr>
</tbody>
</table>

Factors that affect enzyme-catalyzed reactions

• Substrate concentration
• Enzyme concentration
• Temperature
• pH
• Salt concentration (not discussed here)
• Cofactors
• Inhibitors
• Activators
* Substrate Concentration *

- As substrate conc. increases, the reaction rate increases
- When enzyme is **saturated**, rxn rate will reach maximum
  - When this occurs, can increase rxn rate by incr. amt. of enzyme

* Enzyme Concentration *

- As enzyme conc. increases, the reaction rate increases (assuming substrate is abundant)
- Why? *As # molecules increases, there are more collisions, increasing the likelihood that an enzyme will collide with a substrate*
- How is this different from an increase in substrate conc?
  *Theoretically no limits to rate of reaction when adding enz.*
* Temperature *

- As temp incr., so does the rxn rate, *until* enzyme begins to **unfold** or **denature**.

- Every enzyme has an **optimal temp** at which it works best.
- Most human enzymes have an optimal temp range from **35-40°C**.
  - recall human body temp = **37°C**

**Temp-sensitive Enzymes in Siamese Cats**

Dark pigment (melanin) is produced by the following pathway in cats: **Tyrosine --- Intermediate --- Melanin**

The first step of this pathway is catalyzed by the enzyme **tyrosinase**. Siamese cats produce a temperature-sensitive version of tyrosinase, which only functions in cooler temps. This limits the production of melanin to the cooler extremities (ears, nose, paws, tail), resulting in the characteristic Siamese fur coloring.
Temp-sensitive Enzymes in Seals

Newborn seal pups are born with white fur…but their moms have dark fur coats.

When this baby seal grows up, it will grow a darker coat. How is this possible?

Harp Seal Pup Coat Color

1 day old “yellowcoat”

4 day old thin “whitecoat”

7 day old fat “whitecoat”

12 day old “graycoat”

21 day old “ragged jacket”
* pH *

- Every enzyme has an **optimal pH** (fastest rate)
- This optimum is closely related to the pH of the environment the enzyme usually functions/exists in
  - Most mammalian enzymes function best at a pH of about 7 to 8, similar to the cellular environment they are found in
  - Some compartments of the body vary from this near-neutral pH however. For ex)
    - **Mouth** is fairly neutral but
    - **Stomach** is highly acidic &
    - **Beginning of Small Intestine** is fairly basic

**pH Primer**

- **pH** is a measure of H⁺ concentration in a solution
- Note that even “pure” H₂O has some H⁺ due to dissociation (breaking apart):
  \[
  \text{H}_2\text{O} \leftrightarrow \text{H}^+ + \text{OH}^-
  \]
  - The concentration of H⁺ in “pure” water is defined as **neutral** (pH 7)
  - At pH 7, the conc of H⁺ = the conc of OH⁻
Acids and Bases

- **Acids** are chemical compounds that increase the $H^+$ conc of a solution:
  $$\text{HCl (in water)} \rightarrow H^+ + Cl^-$$ (strong acid)

- **Bases** are chemical compounds that decrease the $H^+$ conc of a sol’n (often by increasing the $OH^-$ conc):
  $$\text{NaOH} \rightarrow Na^+ + OH^-$$ (strong base)
  $$\text{NH}_3 + \text{H}_2\text{O} \rightarrow \text{NH}_4^+ + \text{OH}^-$$ (weaker base)

- The strength of an acid or base is determined by the extent to which it dissociates (breaks apart) in sol’n. **Strong** acids and bases dissociate completely in sol’n.

**pH Scale**

- pH scale:
  - **0 to 6.9 = acidic** (more $H^+$ than $OH^-$ in solution)
  - **7 = neutral**
  - **7.1 to 14 = basic** (more $OH^-$ than $H^+$ in solution)

- As the pH of a sol’n **decreases**, the $H^+$ conc **increases**.
- Also note: each pH unit represents a tenfold difference in the $H^+$ conc.
pH Changes Can Affect Protein Structure

- pH affects the charge of the amino acid R groups at the active site, so the properties of the active site change and the substrate can no longer bind.
  - For example, a carboxyl (acid) R groups will be uncharged at low pH (COOH), but charged at high pH (COO\(^-\)).

Enzyme “Helpers”: Cofactors

- Many enzymes require the binding of smaller non-protein cofactors to function.
- Cofactors may be:
  - a small metal ion (like Mg\(^{+2}\), Fe\(^{+3}\), Zn\(^{+2}\), Cu\(^{+2}\))
  - an organic molecule (called a coenzyme)
    - Many vitamins are precursors to important cofactors
      - Thiamine (vitamin B\(_1\)), Riboflavin (B\(_2\)), & Niacin (B\(_3\)) are all precursors to metabolically important cofactors (as evidenced by the diseases that result from their deficiency)
Importance of Some B Vitamins

|                  | Vitamin B1                                      | Vitamin B2                                      | Vitamin B3                                      |
|------------------|------------------------------------------------|
| **Function**     | Coenzyme in cellular respiration                | Coenzyme of flavoprotein enzymes in cellular respiration | Precursor to NADH, a coenzyme in cellular respiration |
| **Sources**      | meat, yeast, whole grains, legumes, enriched bread & breakfast cereals | liver, eggs, dairy, meat, fish, enriched bread & breakfast cereals | meat, legumes, whole grains, yeast, milk, enriched bread & breakfast cereals |
| **Deficiency**   | Beriberi: fatigue, weakness, affects peripheral nerves, heart failure | B2 Deficiency: Damage to eyes, mouth, genitals | Pellegra: dermatitis, diarrhea, dementia, death from organ failure |
| **Excess**       | Water soluble & easily excreted                 | Water soluble & easily excreted                 | Water soluble & easily excreted, may cause brief illness in high dosage |

Metabolic Pathways in Living Things

(each dot is a different molecule)

Every reaction on this map has its OWN enzyme! Wasteful? Silly? No! 
*Advantages to this??*

REGULATION is now possible... by turning enzymes “on” or “off”, you can turn pathways (or parts of pathways) on or off, or *turbo boost* synthesis or breakdown, as needed.

Inhibitors & Activators are molecules that bind to enzymes, turning them off & on respectively.
Regulation of Enz Activity: Inhibition

- Enz inhibitors are chemicals which bind to enzymes and decrease the enzyme’s ability to catalyze its reactant(s).
- Enz inhibitors often bind to an enzyme reversibly (bound with weak bonds, can be released), though sometimes they bind irreversibly (covalently).

If both are present, which molecule will the enz bind to, the substrate or the inhibitor?

It DEPENDS!

- Which is more strongly attracted to the enzyme’s active site?
- Which is present in greater concentration?
Competitive & Non-Competitive Inhibitors

- **Competitive inhibitors** bind to the enz active site & block the substrate from binding.
- The effectiveness of competitive inhibition is dependant upon the relative conc of substrate and inhibitor.

- **Non-competitive inhibitors** bind to another part of the enz, causing the protein to **change shape**, thus making substrate catalysis less favorable/likely.
**Competitive Inhibition**

E+S ⇌ ES → E+P

Substrate

Enzyme

Inhibitor

E+I ⇌ EI

Ei

Product

---

**Noncompetitive Inhibition**

E+I ⇌ EI

Enzyme

Inhibitor

Substrate

E+S ⇌ ES → E+P

Enzyme

EI+S ⇌ ESI

ES+I ⇌ ESI

Product

Ki

K1
Many Poisons Are Enzyme Inhibitors

- **Pesticides** DDT & parathion inhibit key enzymes in the nervous system
- Many **antibiotics** inhibit critical bacterial enzymes
  - Penicillin inhibits enzymes bacteria use to make their cell walls
- **Heavy metals** can also bind irreversibly to and inhibit enzyme active sites
  - Toxic lead (Pb), mercury (Hg), and cadmium (Cd) can replace the cofactor Zn$^{+2}$ in many enzymes, including RNA polymerase.
  (the significance of this enzyme will be clear to you later on this year… basically, without it you cannot make any proteins)

Many Drugs/Medicines are Enzyme Inhibitors Also

Examples include many (but not all):
- Chemotherapy drugs
- Anti-viral drugs
- Antibiotics (as mentioned on previous slide)
Inhibition Is an Important Metabolic Control Mechanism

- Not all of a cell’s metabolic pathways are active at any given time (obviously)
- **Cells regulate metabolic pathways by controlling enzyme activity** (basically, turning enzymes “super-on” or “off”)
  - The activity of some enzymes is controlled by certain molecules binding to a specific regulatory (or **allostERIC**) site on the enzyme, distinct / away from the active site.
  - **Allosteric Inhibitors**: Regulatory molec. that bind to enzymes & turn them “off” or decrease their activity.
  - **Allosteric Activators**: Regulatory molec. that bind to enzymes & keep them “on” or increase their activity.

### Allosteric Inhibition

- **Enz vibrates between “Off” and “On” forms**
- **“Off” form of enzyme** binds sites for both substrate and inhibitor
- **Substrate** binding prevents inhibitor from binding
- Allosteric inhibitors bind somewhere other than the active site and lock the enz into **“off” form** (shown in red), which has a low/no attraction to the substrate.
**Allosteric Activation**

*On* form (only) has binding sites for both *substrate* and *activator*

Enz vibrates between “Off” and “On” forms

**Activator** locks enzyme in “On” form

**Feedback Helps Regulate Metabolic Pathways**

- Different molecules can *inhibit* or *activate* an allosteric enzyme, allowing sophisticated control of the rxn rate.
- Enzymes that are regulated this way are often at the start of a long biochemical pathway.
- They are generally activated by the *substrate* of the pathway (*positive feedforward*) and inhibited by the *product* of the pathway (*negative feedback*), thus only turning the pathway on when it is needed.
Metabolic pathways can be controlled by negative & positive feedback, as well as positive feedforward

- **Feedback** is when a molecule that occurs later in a metabolic pathway affects (positively or negatively) a molecule *earlier* in the pathway.
- **Feedforward** is when an earlier molecule affects a *later* one.

In this diagram:
- D inhibits E2
- F activates E4
- E inhibits E1
- A activates E3 & E5