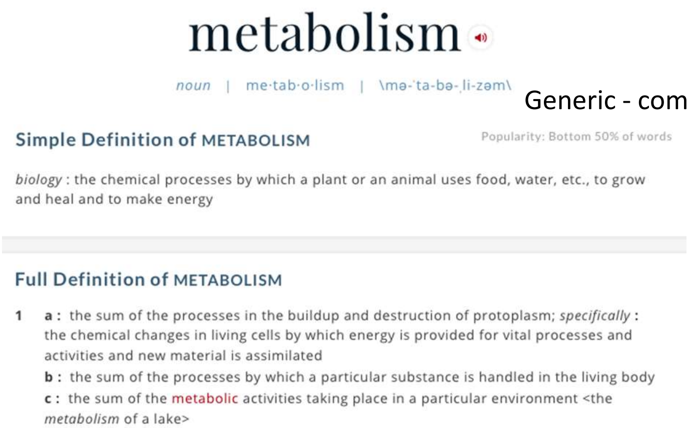
Lec 1 Intro

January 9, 2017 10:05 AM

Why study metabolism?

- To better understand how our own body works.
- To better understand socioeconomic aspects of our society.
  - Obesity crisis
  - Rise in diabetes
- To better understand medical discoveries
  - Diabetes
  - Obesity
  - Genetic metabolic diseases
- Because it will be useful for your future careers in science

What is metabolism?



metabolism

noun | me·tab·o·lism | \mə-ˈta-bə-ˌli-zəm\

Popularity: Bottom 50% of words

Simple Definition of METABOLISM

biology : the chemical processes by which a plant or an animal uses food, water, etc., to grow and heal and to make energy

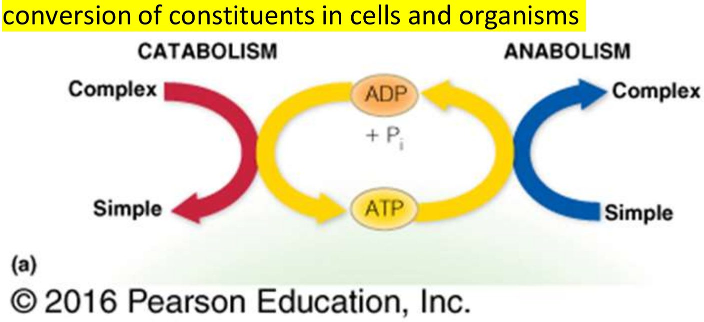
Full Definition of METABOLISM

1 **a :** the sum of the processes in the buildup and destruction of protoplasm; *specifically* : the chemical changes in living cells by which energy is provided for vital processes and activities and new material is assimilated

b : the sum of the processes by which a particular substance is handled in the living body

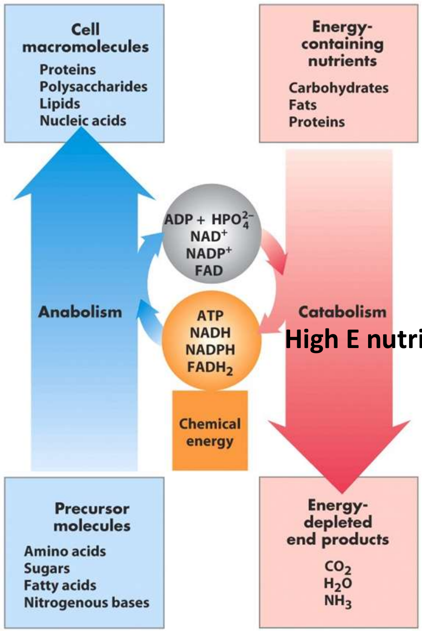
c : the sum of the metabolic activities taking place in a particular environment <the *metabolism* of a lake>

Generic - common ppl

- the sum of biochemical processes involved in the synthesis **(anabolism)**, breakdown (**catabolism**), and inter-conversion of constituents in cells and organisms
- 

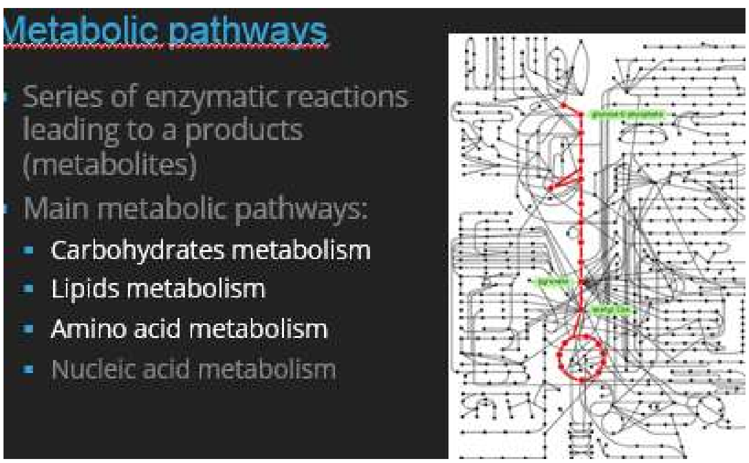
- Balance between the two.

Intermediary Metabolism



Interconversion

- Amino acids will be able to convert into carbohydrates
- Can interconvert molecules
- Missing from figure.



Glycolysis

- Covered this week

- Characteristics?
  - Irreversible
  - Anabolism and catabolism use different pathways
    - Depending on energy demand
    - Allows an independent control
  - Each pathway has a committed step (irreversible reaction)
  - All pathways are regulated
  - Metabolic pathways take places in specific intracellular sites.
    - Intracellular compartmentalization but also at the level of the organs and tissues.

<u>Fundamentals on Metabolism</u>

- Bioenergetics
  - In order to keep our system, cell, organ, body in a steady state, we need:
    - Building blocks (nutrients food)
    - Workers (enzymes and cofactors)
    - Traffic control (compartmentalization, thermodynamics and enzymatic control)

- All this work is made possible using the energy in nutrients to transform it for other purposes.
    - The need for E is constant.
- Energy is provided by electron flow
    - Virtually all energy transductions in cells can be traced to this flow of electrons, from one molecule to another, in a downhill flow from higher to lower electrochemical potential.
    - Oxidation-reduction reactions
        - Where one reactant is oxidized (lose electrons) and another is reduced (gain E-)
- Regulation and control of metabolic pathways
    - To maintain a dynamic steady state and in order to use its available resources efficiently, organisms heavily control how these resources are used.
    - Control measures:
        - Thermodynamics
        - Cell-cell communication and compartmentalization
        - Inhibition and allosteric control
        - Post-translational modifications
        - Enzyme turnover

Control measures: thermodynamics

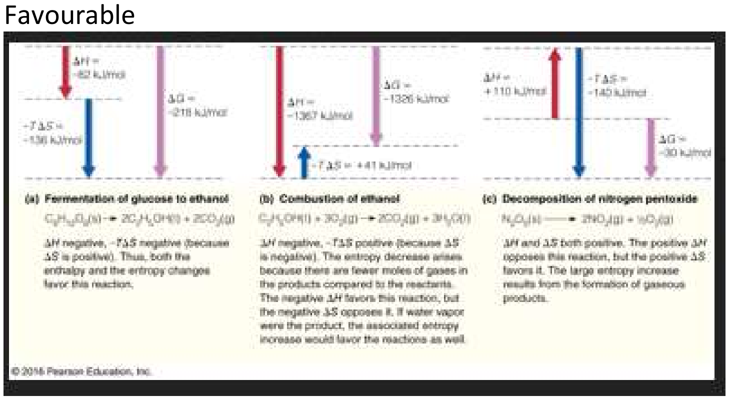
- Free Gibbs energy: $\Delta G = \Delta H - T\Delta S$
- The change in randomness of a reaction or system is expressed as the difference in entropy (ΔS)
- The number and kinds of bonds involved in reaction is the measure of enthalpy (ΔH)
- The measure of total free E capable of doing work for a rxn at constant T and pressure is termed Gibbs free E ΔG)

Favourable /unfavourable

- Synthesis of complex molecules and many other metabolic reactions requires energy (endergonic)
    - A reaction might be thermodynamically unfavorable ($\Delta G > 0$)
        - Creating order requires work and energy
    - Metabolic reaction might have too high energy barrier
        - Metabolite is kinetically stable

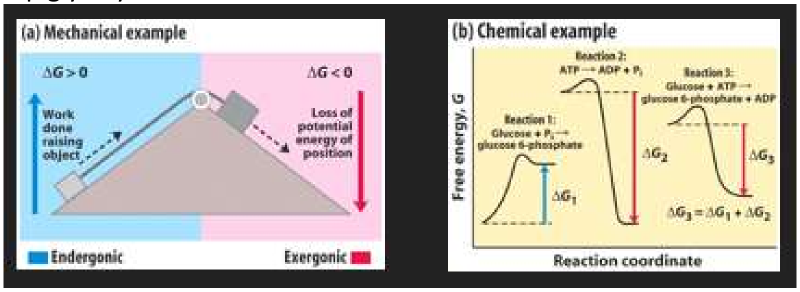
TABLE 3.2 Free energy rules

If ΔG is ...	Free energy is ...	The process is ...
Negative	Available to do work	Thermodynamically favorable (and the reverse process is unfavorable)
Zero	Zero	Reversible; the system is at equilibrium
Positive	Required to do work	Thermodynamically unfavorable (and the reverse process is favorable)

- Breakdown of some metabolites releases significant amount of energy (exergonic)
    - Such metabolites (ATP, NADH, NADPH) can be synthesized using the energy from sunlight and fuels
    - Their cellular concentration is far higher than their equilibrium concentration
    - Will have negative ΔG
- Favourable
    - 

E coupling:

- A thermodynamically unfavorable (endergonic) reaction will proceed in the unfavored direction if it can be coupled to a thermodynamically favorable (exergonic) reaction.

- As long as the exergonic reaction releases more energy than the unfavorable reaction consumes.
    - ΔG of the combined reaction is negative
  - First step glycolysis
    - 

Multiple rxns - E coupling:

- You can COUPLE several reactions together, so that the thermodynamically favourable ones drive the reactions of the thermodynamically UNfavourable ones
- If the SUM of the free energy change is still negative (-ΔG), the reactions are favourable and the exergonic reaction will force the endergonic ones

$$A \xrightarrow[R1]{} B \xrightarrow[R2]{} C \xrightarrow[R3]{} D$$

$$\Delta G_{R1} + \Delta G_{R2} + \Delta G_{R3} = \text{Total } \Delta G$$

$$-30 \quad + \ 45 \quad + -20 \ = -5 = \text{Favorable}$$

Standard Free E Change

- Standard free energy change ($\Delta G^{o\prime}$) is different from actual free energy change (ΔG).
  - Standard free E and Gibbs free E is only the same in ideal conditions
  - The standard free E only takes into account ideal situations
- The standard free energy change ($\Delta G^{o\prime}$) is a constant . It tells us which way the reaction will go in order to reach equilibrium when the initial concentration of each component is 1.0 M, at 25°C, pH 7.0 and constant pressure.
- ΔG depends on actual concentrations of reactants and products, temperature and pressure (R is the gas constant)-
  - $\Delta G = \Delta G^{o\prime} + RT \ln [C][D] / [A][B]$

Organic Phosphate compounds as energy transducers

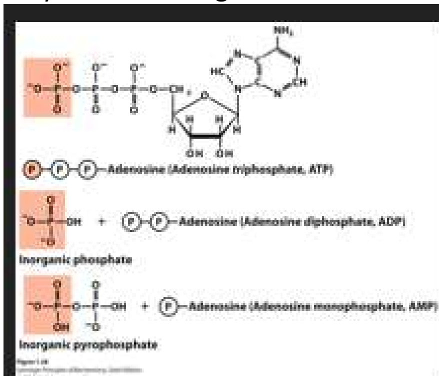
- High E intermediates can be used as E currency,

- **TABLE 3.5** $\Delta G'^{\circ}$ for hydrolysis of some phosphate compounds

Hydrolysis reaction	$\Delta G'^{\circ}$ (kJ/mol)
Phosphoenolpyruvate + H_2O ⟶ pyruvate + P_i	−61.9
1,3-Bisphosphoglycerate + H_2O ⟶ 3-phosphoglycerate + P_i + H^+	−49.4
ATP + H_2O ⟶ AMP + PP_i + H^+	−45.6
Acetyl phosphate + H_2O ⟶ acetate + P_i + H^+	−43.1
Creatine phosphate + H_2O ⟶ creatine + P_i	−43.1
ADP + H_2O ⟶ AMP + P_i + H^+	−32.4
ATP + H_2O ⟶ ADP + P_i + H^+	−32.2
PP_i + H_2O ⟶ 2P_i	−19.2
Glucose-1-phosphate + H_2O ⟶ glucose + P_i	−20.9
Glucose-6-phosphate + H_2O ⟶ glucose + P_i	−13.8

- ATP is E currency, has delta G of -32.2
    - `will be used to make new molecules and push rxn forward
    - ATP is the link between catabolism and anabolism
    - Harvests and uses ATP

Central role of ATP in metabolism
- ATP is:
    - The chemical intermediate linking energy releasing catabolic exergonic reactions with energy demanding anabolic endergonic reactions
- Our bod makes 70 kg of ATP each day
- Rn you have enough ATP for 90 s of regular functions (assuming no new ATP produced.



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PP_i + H_2O ⟶ 2P_i	−19.2
Glucose-1-phosphate + H_2O ⟶ glucose + P_i	−20.9
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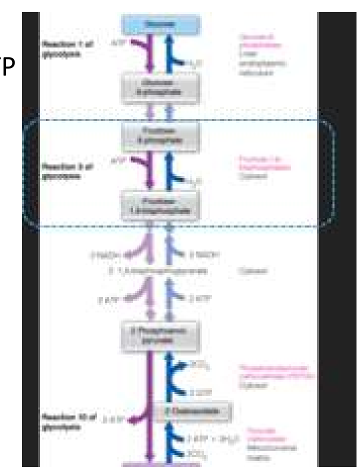
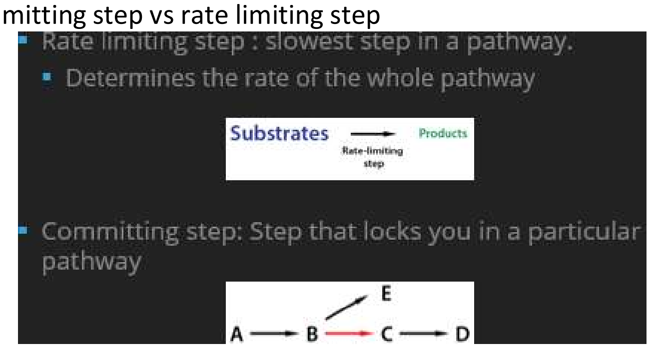
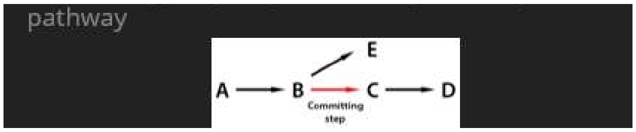
<u>ATP chem currency of E in metabolism</u>

- Hydrolysis of ATP to ADP and Pi has a $\Delta G^{o'}$ of -30.5 kJ/mol (actual DG depends on microenvironment)
- This reaction MUST be coupled to another in order for the energy to be used (and not released as heat!)
- Coupling involves the transfer of these groups from ATP to an enzyme or its substrate ("group transfer reaction")
- Thus, ATP has high "phosphoryl group transfer potential"
    - Will come back to that
    - In cell, have diff sensing proteins that sense level of ATP



<u>Control Measures: Thermodynamics</u>
- Committing step vs rate limiting step
    - 



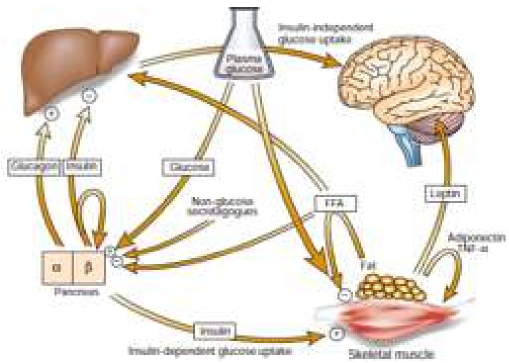
- Sometimes they can be the same
- Like in glycolysis (step #3)

Regulation and control of metabolic pathways

- Control measures:
  - Thermodynamics
  - Cell-cell communication and compartmentalization
  - Inhibition and allosteric control
  - Post-translational modifications
  - Enzyme turnover
- Control measures: Cell - Cell
  - Localization of distinct metabolic pathways: Why?
  - Segregation: Controls metabolic pathways by removing the presence of such and such metabolite or enzyme from
    - Control where rxn is going
- Selective transport: Allows membrane receptors or proteins to control certain steps of a metabolic pathway by letting in or pumping out metabolites or substrates selectively
  - Not covered much in course
- Metabolite sensing: Control of metabolic pathways by enzymes or receptors or osmotic gradients sensing abundance of nutrients, metabolites and substrates
  - Enzyme/receptor sensing - will be covered a lot.
  - Sense E charge, level of ATP in cell.

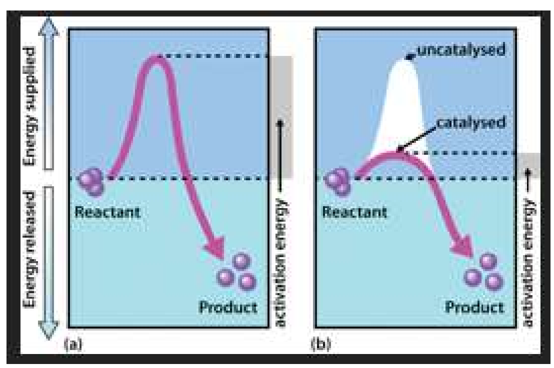
Subcellular fraction	**Pathway**
Mitochondria	TCA cycle Oxidative phosphorylation Fatty acid oxidation Amino acid catabolism
Cytosol	Glycolysis Pentose phosphate pathway Fatty acid biosynthesis Some steps of gluconeogenesis
Lysosomes	Enzymatic digestion of components ingested by endocytosis
Nuclei	Replication and transcription of DNA Maturation of RNA
Golgi apparatus	Post-translational modifications of proteins Membrane assembling

Rough endoplasmic reticulum	Protein synthesis
Smooth endoplasmic reticulum	Lipid biosynthesis
Peroxisomes	Oxidative reactions

- All the diff structures in cell have a role to play.
- Sometimes have choices between going in diff directions bc of the organelles.
- Ex. Insulin
    - 

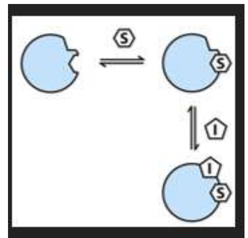
Inhibition and Allosteric Ctrl

- Enzymes catalyze rxns lowering the activation barrier of the rxn process
    - Macromolecules are kinetically stable. Even though their breakdown products are more thermodynamically stable, this kinetic stability forms a barrier for biochemical reactions to occur.
    - Enzymes lower the activation barrier such that the reaction can proceed at much greater speed then would happen naturally.
    - They destabilize the macromolecules, creating a distortion within the structure, lowering the activation barrier.

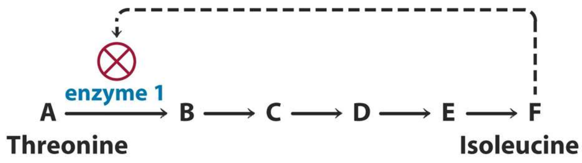


- Inhibition:
    - Endogenous inhibitor
        - End products
    - Exogenous inhibitor
        - Poisons
        - Competitive inhibition:
- Allosteric inhibition (<u>or activation</u>)
    - Binding of a ligand at one site affects binding of another at another site
    - Structural alterations interfere with the accessibility of other ligands, substrates or cofactors, or may disturb the catalytic site.

the catalytic site.


Allosteric inhibition (non-competitive inhibition) or allosteric activation.

- Allosteric inhibition of threonine dehydratase

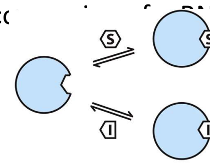


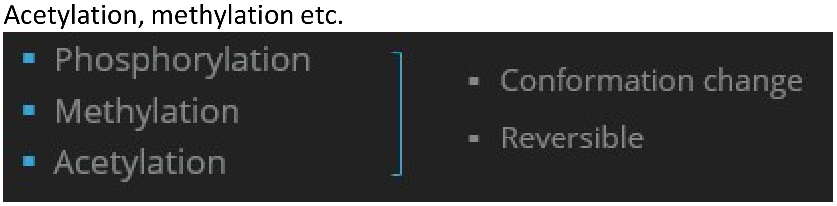
  - E1 = Threonine dehydratase
  - E1 is specifically inhibited allosterically by the end-product F, but by none of the four intermediates (B, C, D, or E).

- Allosteric control
  - 'Allosteric' enzymes exist in at least two different states (controlled by the regulatory substances):
    - R state (R= relaxed): high affinity for substrate
    - T state (T = tense): low or no affinity for substrate
  - Allosteric activators and inhibitors induce conversion from the T to the R state, and the R to the T state, respectively.

Post - translational modifications

- Downstream of the :
  - Transcriptional control: controlling level of mRNA expression.
  - Translational control: at initiation, elongation and termination steps in cc … to protein.
  - They modulate the activities of enzymes already synthesized
  - For acute control of enzyme activities (milliseconds to minutes)
  - Can you identify different types of post-translational modifications?
    - Acetylation, methylation etc.





Enzyme Turnover:

- The ubiquitin pathway is an important component for the control of enzyme turnover.
  - The PEST motif is a tag for the ubiquitination of proteins:

- PEST: proline, glutamic acid, serine, threonine rich sequence
- Proteins with a N-terminal PEST motif “survive” for about 2-3 min
- Proteins lacking a N-terminal PEST motif have half-lives of about 10 hours

Ubiquitin/Proteasome

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