Bil 255 – CMB

the design of metabolism

Cellular energetics & chemical equilibrium
The Design of Metabolism...

Biological Order and Cell Energy Transformations

CELLS Do OBEY LAWS of CHEMISTRY & PHYSICS...
cells possess Potential Energy by having different bonds

2 kinds of traditional energy:
1. **Potential Energy** ... stored energy, due to mass in position
2. **Kinetic Energy** (energy of movement)
   - ex: heat (thermal) energy which flows from higher heat or greater molecular motion to lower heat content;
   - radiant energy kinetic energy of photons (light);
   - when molecules absorb light radiant --> thermal chlorophyll --light--> ATP in photosynthesis
3. **Mechanical energy** - push/pull of cytoskeletal filaments
4. **Electrical energy** - energy of moving electrons
ENERGY in cells is housed in molecules CHEMICAL BONDS. Cells possess Chemical Potential Energy. It occurs in such forms as:

- **Chemical concentrations gradients** across membranes can diffuse from [higher] to [lower]
- **Electrical gradients** (potential differences) across membranes a separation of charge as much as 200,000 volts per cm
THERMODYNAMICS: SCIENCE of ENERGY TRANSFORMATIONS

1st Law of Thermodynamics... Energy can neither be created nor destroyed, but is convertible.

[nuclear blast - mass of U\textsubscript{235} --> heat/light]

all forms of energy are inter-convertible

& thus all are expressed in the same units of measure

Joule, but biologists use more common calorie

calorie is amount of heat needed \(\Delta 1\text{gm} \ 1\degree\text{C}\)

\(1\text{ Kcal} = 1,000\text{ cal} = 4,184\text{ Joule}\) \([1\text{ cal} = 4.184\text{ J}]\)

2nd Law of Thermodynamics… ENTROPY

is commonly referred to as a measure of degree of order of the Universe,

& thus its randomness (Entropy - disorder) can only increase

Entropy is maximum disorder..... "heat"

Events in the Universe have a direction --> max entropy
The Rules of the Universe are simple:
Cities crumble, Stars go Supernova, & we are all equilibrium...izing (dying)

Yet, WOW! … Cells are highly ordered…
  wings of a bird, human eye, spider’s web
  and all cells - feed, grow, and differentiate
HOW… in light of the 2nd law of thermodynamics?

**FOOD** (light energy & covalent bond energy)

Cell reactions = increased order within cell with release of heat

⇒ **HEAT** = overall increased entropy

Entropy must increase (heat); yet disorder within one part of Universe can decrease at the greater expense of the Total Surroundings.
ENERGY IN --> CELL STRUCTURE --> ENERGY OUT

What we need to be able to do is measure Energy in systems, esp. energy able to do work

*Willard Gibbs* (1839-1903) applied the principles of *Thermodynamics* to chemical systems to determine the energy content and changes within a chemical reaction and derived the...

FREE ENERGY EQUATIONS

\[ \Delta G = \Delta H - T \Delta S \]

\( \Delta G \) is a numerical measure of how far a reaction is from equilibrium

\( \Delta G \) is measure amount energy in system able to do work

(to stay away from equilibrium)...

Disorder increases (thus entropy increases) when useful energy, that which could be used to do work, is dissipated as heat...

biological systems are are ISOTHERMAL,

e.g., held at constant temp/pressure

\( (4^\circ \text{ to } \approx 45^\circ) \) and thus \( \Delta H = 0 \)

design of metabolism

Mallery 6
What Gibbs showed was that...

"cell chemical systems change, so that Free Energy is minimized"

thus, \( \Delta G \) can PREDICT..... the Direction of Cellular Reactions......
TOWARD EQUILIBRIUM and to Maximum ENTROPY

Any natural process occurs spontaneously, if and only if,
the associated change in G for the system is negative (\( \Delta G < 0 \)).
when \( \Delta G \) is negative a reaction is spontaneous, R --> P,
& there is a decrease in entropy

Likewise, a system reaches equilibrium when the associated change in G
for the system is zero (\( \Delta G = \) zero),

& no spontaneous process will occur, if the change in G is \textbf{positive} (\( \Delta G > 0 \)).
CHEMICAL REACTION  A <---> B  Which Way?

J. Willard Gibbs (1839-1903)

\[ \Delta G = \Delta G_0' + R \cdot T \cdot \ln \left( \frac{p}{r} \right) \]

change in free energy content of a reaction...depends upon:

1. energy is stored in molecule's covalent bonds
2. remember, temperature is negligible... cells are isothermal, i.e.,

\[ \Delta G = \text{actual free energy} \]
\[ \Delta G_0' = \text{standard free energy [change under std conditions]} \]
\[ R = \text{gas constant (} 2 \times 10^{-3} \text{ Kc/mol)} \]
\[ T = \text{absolute temp (-273} \text{oK)} \]
\[ \ln = \text{natural log (conversion log}10 = 2.303) \]

at equilibrium  \( \Delta G = 0 \) and  \([p]/[r] = \text{Keq} \)
if we solve above equation for \( \Delta G_0' \) we can see \textit{relationship*} of Keq to \( \Delta G_0' \)
Free Energy Equation...

\[ \Delta G = \Delta G^0' + RT \ln \frac{[P]}{[R]} \]

@ equilibrium \[ \Delta G = 0 \]

thus rearranging \[ \Delta G^0' = -RT \ln \frac{[P]}{[R]} \]

@ equilibrium \[ \frac{[P]}{[R]} = Keq \]

@ 250C \begin{align*}
-RT \ln Keq &= -(2.0)(298)(2.303) \log_{10} Keq \\
\text{thus} & \quad \Delta G^0' = -[1364] \log_{10} Keq
\end{align*}
The difference between...  $\Delta G$ and $\Delta G^0$

$\Delta G^0$ is a fixed value for a given reaction & indicates in which direction that reaction will proceed under standard conditions. Standard condition do not exist within a cell, thus $\Delta G$ cab be used to predict the direction of a reaction at a given time.

$\Delta G$ is determined by the concentrations present at that time & is a measure of how far a reaction is from equilibrium then. Cell metabolism is essentially a non-equilibrium condition. Metabolism works by changing the relative concentrations of reactants & products to favor the progress of unfavored reactions.
<table>
<thead>
<tr>
<th>products</th>
<th>reactants</th>
<th>$K_{eq}$</th>
<th>$\lg_{10}$</th>
<th>$\Delta G^0$ cal/mole $[\lg_{10} \times -1364]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1000</td>
<td>.001</td>
<td>$10^{-3}$</td>
<td>-3</td>
<td>+4092</td>
</tr>
<tr>
<td>1/100</td>
<td>.01</td>
<td>$10^{-2}$</td>
<td>-2</td>
<td>+2728</td>
</tr>
<tr>
<td>1/10</td>
<td>.1</td>
<td>$10^{-1}$</td>
<td>-1</td>
<td>+1364</td>
</tr>
<tr>
<td>1/1</td>
<td>1.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10/1</td>
<td>10</td>
<td>$10^{+1}$</td>
<td>+1</td>
<td>-1364</td>
</tr>
<tr>
<td>100/1</td>
<td>100</td>
<td>$10^{+2}$</td>
<td>+2</td>
<td>-2728</td>
</tr>
<tr>
<td>1000/1</td>
<td>1000</td>
<td>$10^{+3}$</td>
<td>+3</td>
<td>-4092</td>
</tr>
</tbody>
</table>

$$[R] > [P]$$

$$[R] = [P]$$

$$[P] > [R]$$

design of metabolism

Mallery

11
Which way this reaction goes is dependent upon existing concentrations?

\[ \Delta G^0' \text{ @ cell [equilibrium]} = \text{K}_\text{eq} \text{ DHAP/G3P} = 22.4 \]

\[ \Delta G^0' = -[1364] \log_{10} 22.4 = -[1364] \log_{10} 1.35 = -1842 \text{ cal/mole} \]

\[ \Delta G = \Delta G^0' + RT \ln[P]/[R] \quad \text{but when DHAP} = 0.001M \quad \text{& G3P} = 0.1M \]

\[ \Delta G = -1842c/m +(-1364)(\log_{10} 0.01) = (-1842)+(-1363)(-2) = +886 \text{ c/m} \]

Thus under standard condition the reaction is favored from G3P toward DHAP (-\(\Delta G\)),

but under specific cellular condition, where the ratio of reactant & products is changed,

the reaction isn't favored & goes in other direction from DHAP to G3P

This is what happens in glycolysis*,

but the pathway shifts ratios and pulls it to G3P
CHEMICAL REACTIONS  \( A \rightleftharpoons B \)  Which way & Why?

**EXERGONIC REACTION** - is one which releases free energy

\[
\text{Product} \ [B] \quad \text{<<< energy} \quad \text{Reactant} \ [A] \quad \text{[stored in covalent bonds]}
\]

ex: burning wood (cellulose)

  glucose monomers = potential energy
  breaks bonds, release heat & light ---> CO\(_2\) & H\(_2\)O

  cell respiration - (heterotrophy) - cellular burning of glucose
  slower, multi-step process to capture & release
  energy.... as ATP

**ENDERGONIC REACTION** - requires input of energy for \( A \rightleftharpoons B \)

\[
\text{Product} \ [B] \quad \text{>>> energy} \quad \text{Reactant} \ [A]
\]

ex: photosynthesis - (autotrophy)

  glucose made from CO\(_2\) + H\(_2\)O --light---> C\(_6\)H\(_{12}\)O\(_6\)
  energy poor vs. energy rich
How does Metabolism create more order in chemical reactions?

**COUPLED REACTION via ATP hydrolysis:**

if $\Delta G$ for the reaction $B + C \rightarrow D$ is $+$,
but less than the $\Delta G$ of ATP hydrolysis,
then the reaction can be driven to completion by coupling it to the hydrolysis of ATP.

ATP hydrolysis energy can be coupled to:

*conformational changes* in enzyme,
as kinases, which phosphorylate proteins (*add --P*)
converting then from inactive to active (& vice versa);

energy gained in the stressed conformation is released,
when the protein relaxes.
Design of Metabolism:

2 Categories of metabolic reactions

[enzyme catalyzed metabolic pathways]  fig 3.2

Anabolic - biosynthesis in autotrophs

coupling reactions that are energetically unfavorable
with reactions that are energetically favored

done by linking hydrolysis of ATP (favored) to reactions
linking atoms together (not favored), creating new biological order
Design of Metabolism:

**Catabolic** - cell respiration in heterotrophs  \( \text{fig 3.3} \)

oxidation (removal) of e-‘s from foodstuffs

3 steps:

1. Digestion of polymers (foods) into monomers
2. GLYCO-LYSIS \( \text{--->} \text{AcoA} \) splits sugar monomers
3. Oxidation of AcoA \( \text{--->} \text{CO}_2 + \text{NADH} \text{--->} \text{H}_2\text{O} \)
   \( \text{ADP} + \text{P} \text{--->} \text{ATP} \)

FREE ENERGY EQUATIONS \( \Delta G = \Delta H - T \Delta S \)

a numerical measure of how far a reaction is from equilibrium
Design of Metabolism... or how biological order comes about
Organisms are classified by the nutritional habits...

**Autotrophs:**
light energy... is converted into covalent chemical bond energy

\[
\begin{align*}
    & e^- & H_2O & \xrightarrow{H^+} & NADPH + ATP \\
    & CO_2 & \xleftarrow{\uparrow} & \text{oxidized form} \\
    & CH_2O & \xleftarrow{\downarrow} & \text{reduced form}
\end{align*}
\]

**Heterotrophs:**
food stuffs more energetically stable

\[
[CH_2O]_n + NAD^+ \xrightarrow{\downarrow} CO_2 + H_2O + ATP + NADH
\]

Key Cell energy intermediates - NADH & NADPH, FAD, & ATP*

design of metabolism

Mallery 17
(a) Oxidized: NAD$^+$  
\[
\text{Nicotinamide} + \text{Ribose} + 2\text{P} \quad \xrightarrow{\text{ADP}} \quad \text{Adenosine}
\]

Reduced: NADH  
\[
\text{Ribose} + 2\text{P} \quad \xrightarrow{\text{ADP}} \quad \text{Adenosine}
\]

\[\text{NAD}^+ + \text{H}^+ + 2\text{e}^- \quad \xrightarrow{\text{ADP}} \quad \text{NADH}\]

(b) Oxidized: FAD  
\[
\text{Flavin} + \text{Ribitol} + 2\text{P} \quad \xrightarrow{\text{ADP}} \quad \text{Adenosine}
\]

Reduced: FADH$_2$  
\[
\text{Ribitol} + 2\text{P} \quad \xrightarrow{\text{ADP}} \quad \text{Adenosine}
\]

\[\text{FAD} + 2\text{H}^+ + 2\text{e}^- \quad \xrightarrow{\text{ADP}} \quad \text{FADH}_2\]

\[\text{H}_2\text{O} + \text{Triphosphate} \quad \xrightarrow{\Delta G'' = -7.3 \text{ kcal/mol}} \quad \text{Adenosine triphosphate (ATP)}\]

\[\text{Adenine} + \text{Ribose} \quad \xrightarrow{\Delta G'' = +7.3 \text{ kcal/mol}} \quad \text{Adenosine diphosphate (ADP')}\]

\[+ \text{Inorganic phosphate (P$\text{i}$)}\]

Copyright 1969 John Wiley and Sons, Inc. All rights reserved.

design of metabolism  
Mallery  
18
Design of metabolism...

**OXIDATION / REDUCTION - Redox Reactions**

- e- &/or H+ transferred between oxidized & reduced forms
  
  \[ AH \underset{\text{oxidation}}{\overset{\text{reduction}}{\rightleftharpoons}} A + e^- + H^+ \]

- **oxidation** - removal of e- from substrate
- **reduction** - gaining of e- (& often a proton, H+)

\[
6\text{O}_2 + C_6\text{H}_{12}\text{O}_6 \overset{\text{respiration}}{\rightleftharpoons} 6\text{CO}_2 + 6\text{H}_2\text{O}
\]

\[
\overset{\text{photosynthesis}}{\rightleftharpoons}
\]

\[
6\text{O}_2 + C_6\text{H}_{12}\text{O}_6 \overset{\text{photosynthesis}}{\rightleftharpoons} 6\text{CO}_2 + 6\text{H}_2\text{O}
\]

**fig 3.12**

**fig 3.10**
KEY METABOLIC REACTIONS:

6 major categories of bio-chemical reactivity
Bio-chemical reactivity is bond breaking & reforming
these are violent events inside cells, carefully controlled by ENZYMES

1. redox reaction (oxid/reduction)  PGAld + NAD+  -->  1,3di-PGA + NADH
oxidoreductases (dehydrogenases)
2. functional group transfers  glu + ATP  -->  G6P + ADP
transferases
3. Hydrolysis  glu-glu(n) + H₂O  -->  glu-glu(n-1)
hydrolyases
4. C-C breaking or re-formation  fruc1-6bP  -->  DHAP + 3PGAld
lyases
5. rearrangement (isomerizations)  glucose-6P  -->  fructose-6P
isomerases
6. Condensations  protein(n) + aa1  -->  protein(n+1) + H₂O
transferases