Energy, thermodynamics, and molecular processes

Overview

Leading question: do cells use energy?

Cells consume negative entropy, i.e., generate positive entropy

Life = negative entropy generation

Cells are bound by the laws of thermodynamics? Yes

The central question is: how can complex, seemingly highly ordered processes and biological structures emerge "spontaneously" in living things

Review of thermodynamics

What do we need to do here? Cells are very small, so we need to understand thermodynamics at a molecular level. This is somewhat different than thermodynamics for macroscopic systems.

In macroscopic, bulk systems, everything appears to be constant – the density, temperature, pressure, heat capacity, etc. At the molecular level, however, there is a constant molecular dance and things **fluctuate**. We don't notice these fluctuations at the macroscopic level because they are so small.

Example: the density in a fluid.

The first law

Thermodynamics defines a system and an environment, separated by a system boundary

The **first law** is a statement of the conservation of energy for a **process** that involves a change to the system

Here we consider closed systems for simplicity, although living systems are certainly open

Closed systems = those with no mass exchange with the environment, but can exchange energy

Differential form (small changes) for closed systems:

$$dU = \delta Q + \delta W$$

Integrated form (state changes) for closed systems:

$$\Delta U = Q + W$$

Here,

- U is the total internal energy in the system. In other words, it is the total potential energy due to molecular interactions as well as kinetic energy due to the velocities of the molecules
- Q is the heat exchanged with the environment; it comes from energies stored in random molecular motions → positive for heat added to system
- W is the work done on the system; it comes from energies due to concerted molecular motions → positive for work done on system

We can define pressure-volume work as

$$W = -\int PdV$$

Notice that the internal energy is a property of the system, whereas Q and W describe *flows* between the system and environment

U is a **state function.** Thermodynamics defines s**tate functions** as quantities that depend only on the current state of a system (e.g., T and P), and not the path by which they got there.

Therefore, ΔU does not depend on the path the process takes (e.g., the rate at which it happens), but only on the states at the beginning and end of the process

On the other hand, Q and W are not state functions and do depend on the path

Interestingly, the sum of Q and W is a state function. That means that any path-dependence of these quantities exactly cancels out. There can be many processes that take a system between two states 1 and 2 with very different Q and W, but their sum must be the same.

The second law

Again, here we consider the case of a closed system

The second law states that

$\Delta S \geq 0$ for any spontaneous process in an **isolated macroscopic system**

The entropy is a measure of the number of the number of microscopic states, or **microstates**, that the system has available to it. You can think of a microstate as one configuration of atoms.

$$S = k_B \ln \Omega$$

where k_B is Boltzmann's constant, equal to the gas constant on a per-molecule rather than per-mol basis.

Entropy is also a state function.

We can also measure the change in entropy between two states using a reversible process,

$$\Delta S = \int \frac{\delta Q_{rev}}{T}$$

The second law for systems at constant T and P

What about non-isolated systems? Does the entropy always increase?

Here, we have to consider the surroundings. If the surroundings are large such that we can treat them as a big, constant temperature heat bath, we can write

$$\Delta S_{\text{surr}} = \frac{Q_{\text{surr}}}{T}$$

Here the total isolated system is the surroundings plus the system. Therefore we have

$$\Delta S + \Delta S_{surr} \geq 0$$

$$\Delta S + \frac{Q_{\text{surr}}}{T} \geq 0$$

$$\Delta S - \frac{Q}{T} \geq 0$$

Multiplying by T and using the first law,

$$T\Delta S - (\Delta U - W) \geq 0$$

If we have a constant pressure process,

$$W = -\int P dV = -P \int dV = -P\Delta V = -\Delta(PV)$$

Substituting,

$$T\Delta S - \Delta U - \Delta(PV) \geq 0$$

Alternatively,

$$\Delta U - T\Delta S + \Delta(PV) \leq 0$$

We define the **Gibbs free energy** using

$$G \equiv U - TS + PV$$

Notice that G is a state function since it is a combination of state functions.

Thus we have,

$$\boxed{\Delta G \leq 0}$$

This is a fundamental equation in the thermodynamics of systems that are at constant T and P. It says that

- spontaneous processes always decrease the Gibbs free energy of a system
- the system is at a minimum value of the Gibbs free energy at equilibrium
- processes always tend towards free energy minima

Other state functions and thermodynamic variables

We also have the **enthalpy**

$$\begin{aligned} H &\equiv U + PV \\ &= G + TS \end{aligned}$$

And the Helmholtz free energy

$$\begin{aligned} A &\equiv U - TS \\ &= G - PV \end{aligned}$$

The heat capacities of the system can be related to changes in U and H at different conditions

$$C_V \equiv \left(\frac{dU}{dT}\right)_V = T\left(\frac{dS}{dT}\right)_V \qquad C_P \equiv \left(\frac{dH}{dT}\right)_P = T\left(\frac{dS}{dT}\right)_P$$

Microscopic origins of thermodynamics

Statistical mechanics provides a microscopic (molecular) basis for the thermodynamic laws that we know and love

You've already seen one aspect, $S = k_B \ln \Omega$

We won't pursue a detailed treatment of statistical mechanics, but rather one main aspect

- At equilibrium, the molecules of a system are constantly moving around

- We can't pinpoint the specific configuration or microstate that the system will be in
- We can however determine the probability with which we would find the system's molecules in a particular *collective* configuration.
- This probability is equivalent to the fraction of time the system spends in that configuration.

Statistical mechanics says that the probabilities of microstates follow the Boltzmann distribution. Consider a particular configuration of atoms denoted by m. The probability of that **configuration** is given by

$$\wp_m \propto e^{-\frac{U_m}{k_B T}}$$

Here, U_m is the energy of the configuration m. One could determine it by examining all of the interactions present, e.g., hydrogen bonds, vdW, electrostatic, etc.

This expression implies a constant of proportionality. Let's rewrite it with that constant, C,

$$\wp_m = Ce^{-\frac{U_m}{k_B T}}$$

How do we determine the constant of proportionality? Simple… we demand that the probabilities sum to one.

$$\sum_m \wp_m = 1$$

$$\sum_m Ce^{-\frac{U_m}{k_B T}} = 1$$

$$C\sum_m e^{-\frac{U_m}{k_B T}} = 1$$

$$C = \left(\sum_m e^{-\frac{U_m}{k_B T}}\right)^{-1}$$

Therefore, if we have 10 configurations, the probability of configuration 1 is given by

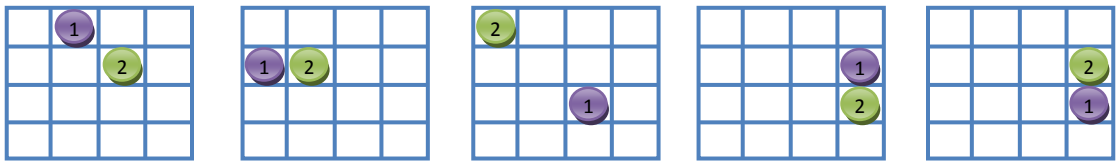
$$\wp_1 = \frac{e^{-\frac{U_1}{k_B T}}}{e^{-\frac{U_1}{k_B T}} + e^{-\frac{U_2}{k_B T}} + \cdots + e^{-\frac{U_{10}}{k_B T}}}$$

Therefore, to derive the probabilities of a system, we need to have a list of all possible configurations and their energies so that we can perform the sum in the denominator.

Example

Two molecules are adsorbed on a two-dimensional cell surface, which we will describe as a lattice. There are M total lattice sites where the molecules can adsorb. If the two molecules are at adjacent sites, van der Waals interactions between them result in a negative potential energy in the amount of $-\epsilon$; otherwise, the molecules do not interact. What is the probability that the molecules will be in contact at a given temperature T?

For this problem, we have to think about what microstates are possible in the system. Here are some possibilities for a system with $\mathrm{M} = 16$:



$U = 0$ $U = -\epsilon$ $U = 0$ $U = -\epsilon$ $U = -\epsilon$

We notice that each lattice site has a total of four neighbors, with the exception of the edge sites. However, the number of edge sites will be much less than the total number of sites M if M is large, therefore we can neglect this subtle effect.

First, count the total number of states. There are $M(M-1)$ of them.

The probability of states 2, 4, 5, and any other "bound" states is

$$\wp \propto e^{\frac{\epsilon}{k_B T}}$$

The probability of all other states is

$$\wp \propto e^{-\frac{0}{k_B T}} = 1$$

To figure out the sum needed to normalize the probabilities, we need to know how many bound and unbound microstates there are. The number of possible $\mathrm{E} = -\epsilon$ microstates is just the total number of ways we can place the first molecule times the number of possible neighbors to it:

$$\#\text{ bound states} = \mathrm{M} \times 4$$

On the other hand, the total number of configurations is just the M number of spots to put the first molecule, times the $(\mathrm{M}-1)$ number of spots to then place the second. Therefore,

$$\#\ \text{unbound states} = \mathrm{M}(\mathrm{M}-1) - 4\mathrm{M}$$

Therefore the normalization factor is

$$4Me^{\frac{\epsilon}{k_BT}} + (M^2 - 5M)$$

The probability that the molecules are bound is the sum of all the probabilities for each of the bound microstates. There are 4M of these:

$$\wp(bound) = 4M \times \frac{e^{\frac{\epsilon}{k_BT}}}{4Me^{\frac{\epsilon}{k_BT}} + (M^2 - 5M)}$$
$$= \left[1 + \frac{M-5}{4} e^{-\frac{\epsilon}{k_BT}}\right]^{-1}$$

Examine temperature limits.

Role of free energies

Sometimes we don't care about the probability of an individual configuration, but rather, the probability of some state that could be one of many configurations.

In the last example, we were only interested in the bound and unbound states. For each of these, we could have one of many configurations.

We might have written

$$\wp(bound) \propto \Omega(bound)e^{\frac{\epsilon}{k_BT}}$$

where $\Omega(bound)$ gives the number of configurations for the bound state. Similarly,

$$\wp(unbound) \propto \Omega(unbound)e^{0}$$

We can then write the absolute probabilities as

$$\wp(bound) = \frac{\Omega(bound)e^{\frac{\epsilon}{k_BT}}}{\Omega(bound)e^{\frac{\epsilon}{k_BT}} + \Omega(unbound)e^{0}}$$

But note that $\Omega(bound) = e^{\frac{S(bound)}{k_BT}}$ by Boltzmann's law. Therefore, we could write:

$$\wp(bound) \propto \exp\left[\frac{S(bound)}{k_B} - \frac{U(bound)}{k_BT}\right]$$

where $U(bound) = -\epsilon$. The combination of S and U in this fashion should be familiar. Note that $A = U - TS$ for the Helmholtz free energy. Therefore, we can write

$$\wp(bound) \propto \exp\left[-\frac{A(bound)}{k_B T}\right] \qquad A(bound) = U(bound) - TS(bound)$$

Similarly,

$$\wp(unbound) \propto \exp\left[-\frac{A(unbound)}{k_B T}\right] \qquad A(unbound) = U(unbound) - TS(unbound)$$

Even though this is a specific example, there is an underlying general trend here:

The probability of seeing a state that may correspond to many configurations relates to the free energy of that state

$$\wp(state) \propto \Omega(state) \exp\left[-\frac{U(state)}{k_B T}\right]$$
$$= \exp\left[-\frac{A(state)}{k_B T}\right]$$

That is, free energies dictate populations at equilibrium.

Notice that if the state consists of only one configuration, $\Omega = 1$ and $S = 0$ such that $A = U$ and we recover the usual Boltzmann law.

The previous results apply to the case in which our system is at constant volume. However, most processes are at constant pressure. In this case, the rule uses the Gibbs rather than the Helmholtz free energy because of the inclusion of PV work in the energies:

At constant pressure,

$$\wp(state) \propto \exp\left[-\frac{G(state)}{k_B T}\right]$$

This important equation will be useful for understanding the equilibrium properties of molecules in cells. In particular, it will tell us the fraction of the time that molecules spend in one conformation or interaction mode versus another.

Units

Note the similarity between k_B and R, the ideal gas constant:

- k_B is on a per-molecule basis

- R is on a per-mole basis

$$k_B N_A = R$$

When using these expressions it is vital that the constant used has the same units as that of the free energy.

If $G(state)$ quoted in per-molecule units, use:

$$\wp(state) \propto \exp\left[-\frac{G(state)}{k_B T}\right]$$

If $G(state)$ quoted in per-mol units, use:

$$\wp(state) \propto \exp\left[-\frac{G(state)}{RT}\right]$$

Keep in mind that if you match units correctly (mol-mol and molecule-molecule) you should not have trouble. For the remainder of this lecture we will take the per-mol convention:

$$\wp(state) \propto \exp\left[-\frac{G(state)}{RT}\right]$$

Microscopic dynamics and diffusive processes

Are cells at equilibrium? Not really, but equilibrium is still relevant

- driving forces for processes (minimizing free energies)
- quasi-equilibrium in many respects

Thermodynamics says nothing about kinetics, but it places limits on the kinds of processes that can occur

Here we consider basic, undriven molecular motion, typical of the kind you might find for a system at equilibrium

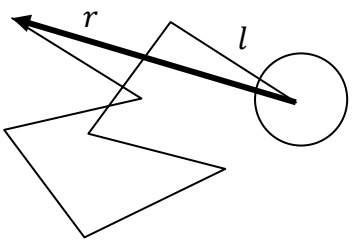
- undriven – no change in free energies during process
- molecular motion – molecules are constantly moving about, even at equilibrium

Random walk

Consider a sea of molecules. Pinpoint one molecule and note its starting position at time 0.

Due to thermal motion, the particle on average makes a random jump of length l every τ units of time. The jump is random in the radial direction. This is called a **random walk**.

Repeat this process for many jumps n and interrogate the final distance of the particle from its starting point



We could imagine doing many such experiments. What would be the expected $\langle x \rangle$, $\langle y \rangle$, $\langle z \rangle$ as a function of n?

$$\langle x \rangle = 0 \quad \langle y \rangle = 0 \quad \langle z \rangle = 0$$

since the process is spherically symmetric.

What about $\langle r_n^2 \rangle$?

$$r_n^2 = x_n^2 + y_n^2 + z_n^2$$

Consider the case in going from step n to n+1:

$$\begin{aligned} r_{n+1}^2 - r_n^2 &= x_{n+1}^2 - x_n^2 + y_{n+1}^2 - y_n^2 + z_{n+1}^2 - z_n^2 \\ &= (x_n + \Delta x)^2 - x_n^2 + (y_n + \Delta \mathrm{y})^2 - y_n^2 + (z_n + \Delta z)^2 - z_n^2 \\ &= (x_n + \Delta x)^2 - x_n^2 + (y_n + \Delta \mathrm{y})^2 - y_n^2 + (z_n + \Delta z)^2 - z_n^2 \\ &= 2x_n \Delta x + \Delta x^2 + 2y_n \Delta y + \Delta y^2 + 2z_n \Delta z + \Delta z^2 \end{aligned}$$

Here, $\Delta x, \Delta y, \Delta z$ are the random amounts by which we change the length at one step. Notice that we have the constraint $\Delta x^2 + \Delta y^2 + \Delta z^2 = l^2$. Therefore

$$r_{n+1}^2 - r_n^2 = 2x_n \Delta x + 2y_n \Delta y + 2z_n \Delta z + l^2$$

Now, we average over all possible (random) trajectories for the same starting point:

$$\langle r_{n+1}^2 - r_n^2 \rangle = \langle 2x_n \Delta x + 2y_n \Delta y + 2z_n \Delta z \rangle + l^2$$

However, since the $\Delta x, \Delta y, \Delta z$ are random with zero mean, and uncorrelated to the current position of the molecule, the average on the RHS becomes

$$\langle r_{n+1}^2 - r_n^2 \rangle = l^2$$

Or

$$\langle r_{n+1}^2 \rangle = \langle r_n^2 \rangle + l^2$$

By recursion, therefore, we can write

$$\begin{aligned} \langle r_n^2 \rangle &= nl^2 \\ &= \frac{t}{\tau} l^2 \end{aligned}$$

The LHS is called the **mean squared displacement**. It tracks the average squared distance of a particle at time zero from its random location at time t.

This kind of random movement is called **Brownian motion** and is a kind of **diffusive** process. Here, diffusive means that the motion is dominated by random fluctuations. In contrast, **activated** processes require concerted movements over free energy barriers.

In fact, we can define the diffusion constant $D \equiv \frac{l^2}{6\tau}$. Then,

$$\langle r^2 \rangle = 6Dt$$

In the limit that both the step length and the step time go to zero, the random walk can be described by the diffusion equation:

$$\begin{aligned} \frac{\partial \wp(x,y,z,t)}{\partial t} &= D\left(\frac{\partial^2 \wp(x,y,z,t)}{\partial x^2} + \frac{\partial^2 \wp(x,y,z,t)}{\partial y^2} + \frac{\partial^2 \wp(x,y,z,t)}{\partial z^2} \right) \\ &= D\nabla^2 \wp(x,y,z,t) \end{aligned}$$

Here, $\wp(x,y,z,t)$ gives the probability a molecule is at location x, y, z at time t. You can think of it in the same sense as a concentration.

Activated processes and reaction kinetics

In contrast to diffusive processes, **activated processes** have a free energy barrier that prevents them from occurring spontaneously.

Consider a typical reaction in which a molecule A converts to a type B. This could be a chemical reaction, in which bonds break and form, or it could be a physical reaction, in which B is some conformational change of the molecule, e.g., rotation around a bond.

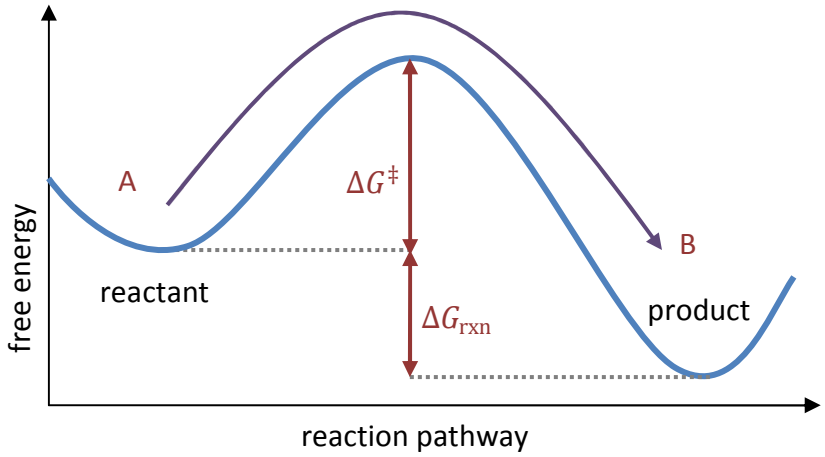
$$A \rightarrow B$$

Recall the conditions at which the reaction will move forward. Thermodynamics says that for process to spontaneously occur, the net effect of the reaction must be a decrease in free energy.

$$\Delta G_{rxn} < 0 \rightarrow \text{ reaction moves forward}$$

$$\Delta G_{rxn} > 0 \rightarrow \text{ reaction will not move forward}$$

Even if the reaction moves forward, in activated processes it takes some time. We can understand this effect with a typical reaction state diagram:



Associated with this reaction is a free energy barrier that occurs at the **transition state**.

In order for the reaction to occur, the system has to spontaneously increase its free energy enough to surmount the barrier. This requires a rare **fluctuation** in energies at the molecular level. The higher the barrier, the rarer the fluctuation and the longer the time it takes for the process to occur.

Wait? How can the free energy increase? It does so only in small increments at the molecular level. This is not a violation of the second law, since small fluctuations in the free energy are allowed such that the average free energy, averaged over many molecules, does decrease.

Transition states and reaction rates

The rate at which the reaction occurs is given by

$$\text{reaction rate} = -\frac{d[A]}{dt} = k[A]$$

Here, the reaction rate constant is given by

$$k = k_0 e^{-\frac{\Delta G^{\ddagger}}{RT}}$$

if ΔG is given in units per molecule. If it is instead given in units per mol, we use R instead of k_B.

Why does the rate equation have this form? Recall that the probability of a particular state is given by

$$\wp(state) \propto e^{-\frac{G(state)}{RT}}$$

The ratio of the probability to be at the transition state versus the initial state is

$$\frac{\wp(ts)}{\wp(A)} = \frac{e^{-\frac{G(ts)}{RT}}}{e^{-\frac{G(A)}{RT}}} = e^{-\frac{\Delta G^{\ddagger}}{RT}}$$

Thus the rate is related to the probability that the system finds the transition state.

Recall that we can write $\Delta G = \Delta H - T\Delta S$ at constant temperature. Substituting above,

$$k = k_0 e^{-\frac{\Delta H^{\ddagger}}{RT} + \frac{\Delta S^{\ddagger}}{R}}$$

Sometimes the change in entropy between the initial state and the transition state is very small such that we can neglect the second term in the exponential. Under this approximation,

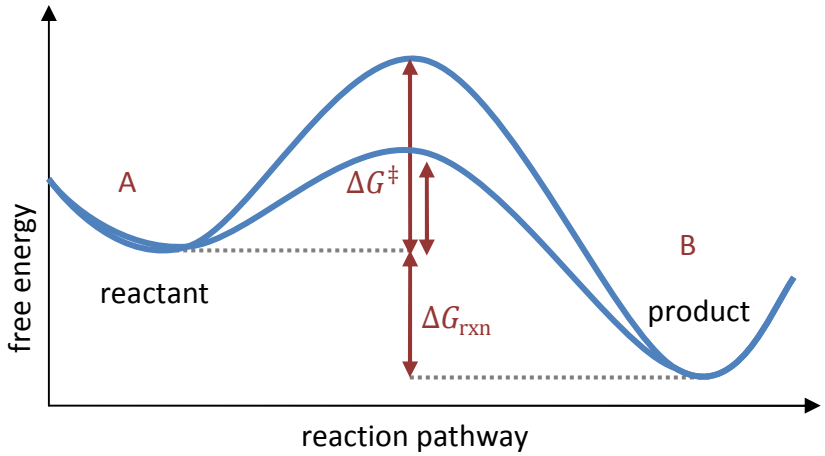
$$k \approx k_0 e^{-\frac{\Delta H^{\ddagger}}{RT}}$$

Catalysis

Many, many reactions in cells are energetically favorable but do not spontaneously occur → would result in chaos!

Instead, **enzymes** act as catalysts to lower the free energy barrier. Enzymes are basically protein catalysts.

Enzymes speed up reactions greatly but also act as regulators of what reactions occur.



Equilibrium constant and free energy of reaction

The above considerations apply to a single reaction event, e.g., single sets of molecules. We typically indicate this with the superscript "o":

$$\Delta G^{\circ}_{rxn}, \Delta H^{\circ}_{rxn}, \Delta S^{\circ}_{rxn}$$

In reality there are concentration effects. How does the free energy depend on concentration?

For dilute systems, we can write:

$$G_A = G^{\circ}_A + k_B T \ln[A]$$

for a species A, where the free energies are on a per-molecule basis. Alternatively

$$G_A = G^{0}_A + RT \ln[A]$$

for a per-mol basis.

Where does this expression come from? Consider,

$$\begin{aligned} \wp(A) &\propto e^{-\frac{G_A}{k_B T}} \\ &= e^{-\frac{G^{\circ}_A}{k_B T}} \times V \\ &= \frac{e^{-\frac{G^{\circ}_A}{k_B T}}}{1/V} \\ &= \frac{e^{-\frac{G^{\circ}_A}{k_B T}}}{[A]} \end{aligned}$$

$$= e^{-\frac{G_A^\circ + k_B T \ln[A]}{k_B T}}$$

Now consider ΔG_{rxn} for $A \rightarrow B$:

$$\begin{aligned}\Delta G_{rxn} &= G_B - G_A \\ &= G_B^\circ - G_A^\circ + k_B T(\ln[B] - \ln[A]) \\ &= \Delta G_{rxn}^\circ + k_B T \ln \frac{[B]}{[A]}\end{aligned}$$

On a per-mol basis:

$$\boxed{\Delta G_{rxn} = \Delta G_{rxn}^\circ + RT \ln \frac{[B]}{[A]}}$$

What if $\Delta G > 0$? What if $\Delta G < 0$?

What happens at equilibrium? Nothing spontaneously happens; nothing changes with time. This means there are no free energy gradients:

$$\Delta G_{rxn} = 0$$

$$0 = \Delta G_{rxn}^\circ + RT \ln \frac{[B]}{[A]}$$

$$\frac{[B]}{[A]} = \exp\left(-\frac{\Delta G_{rxn}^\circ}{RT}\right)$$

But we make the definition

$$\boxed{K_{eq} \equiv \exp\left(-\frac{\Delta G_{rxn}^\circ}{RT}\right)}$$

So that

$$\boxed{\frac{[B]}{[A]} = K_{eq}}$$

How does K_{eq} connect to the reaction rates? At equilibrium, the net reaction from the forward and reverse processes becomes zero:

$$\frac{d[A]}{dt} = -k_f[A] + k_r[B] = 0$$

$$\frac{d[B]}{dt} = k_f[A] - k_r[B] = 0$$

Setting both equal to zero and solving gives

$$\frac{[B]}{[A]} = \frac{k_f}{k_r}$$

Thus we find that

$$K_{eq} = \frac{k_f}{k_r}$$

How does k_r relate to the transition path diagram?

Temperature dependence of free energies

Oftentimes we want to investigate how the free energy of a particular reaction changes with T

$$\Delta G(T) = G_B(T) - G_A(T) = ???$$

Say the heat capacity of species A and B is constant,

$$C_{P,A} = const$$

$$C_{P,B} = const$$

Then it can be shown [first problem set] that the change in free energy has the following T-dependence:

$$\boxed{\Delta G(T) = \Delta H_0 \left(1 - \frac{T}{T_0}\right) + \Delta C_p \left[T - T_0 - T \ln\left(\frac{T}{T_0}\right)\right]}$$

Here we have three parameters, two additional above the heat capacities

$$\Delta C_P \equiv C_{P,A} - C_{P,B}$$

$$T_0 \quad \text{reference temperature at which } \Delta G = 0$$

$$\Delta H_0 \quad \text{enthalpy at } T_0$$

Notice that if the heat capacities are approximately equal between A and B, we have

$$\boxed{\Delta G(T) = \Delta H_0 \left(1 - \frac{T}{T_0}\right)}$$

(Free) energy sources, carriers, and storage in cells

How do living systems perform complex, driven processes?

Answer: they find ways (paths) for the processes that involve continuous decreases in free energy and hence increases in world entropy → called **free energy transduction**

In order for this situation to exist in perpetuity, living systems need sources of high free energy and low entropy

- chemical bonds – food
- sunlight

Photosynthesis generates high-free energy sugars using sunlight:

$$\text{light} + CO_2 + H_2O \rightarrow \text{sugars} + O_2$$

This reaction is spontaneous, i.e., it results in a decrease in free energy and an increase in world energy. Thus, heat is generated.

Cells can then harness energy from sugars through decomposition reactions that are also free-energetically favorable through **glycolysis**:

$$C_6H_{12}O_6(\text{glucose}) + \text{unloaded energy carriers} \rightarrow C_3H_6O_3^- + \text{energy carriers}$$

The energy carriers are specialized molecules—"batteries"—that the cell uses to transport high-free energy packets for use in many, many molecular interactions

Unfavorable reactions

How do we make a free-energetically unfavorable interaction proceed? Many such interactions are required in biology: the synthesis of DNA, RNA, proteins, and sugars all entail increases in free energy

Solution: couple unfavorable reactions with favorable ones so that the net free energy change is negative

Example:

$$A + B \rightarrow AB \quad \Delta G_{AB} > 0$$

We might couple this to a favorable reaction:

$$XY \rightarrow X + Y \quad \Delta G_{XY} < 0$$

How can the coupling be performed? Consider the sequence:

$$A + XY \rightarrow AX + Y \qquad \Delta G_{AXY}$$

$$AX + B \rightarrow AB + X \qquad \Delta G_{AXB}$$

The net result of the two reactions is the same:

$$A + B + XY \rightarrow AB + X + Y \qquad \Delta G_{\text{overall}} = \Delta G_{AXY} + \Delta G_{AXB}$$

Since the beginning and endpoints are the same, the free energy difference is the same as if the two reactions occurred independently:

$$\Delta G_{overall} = \Delta G_{AB} + \Delta G_{XY}$$

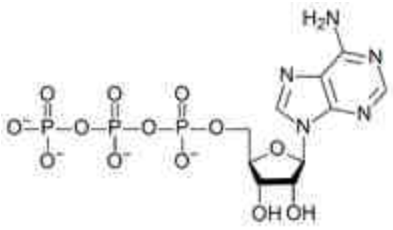
Therefore, the net reaction will proceed if:

- $\Delta G_{AB} + \Delta G_{XY} < 0$
- $\Delta G_{AXY} < 0$
- $\Delta G_{AXB} < 0$

This is how molecules are able to perform free-energetically unfavorable steps.

ATP – the basic energy carrier

Adenosine triphosphate (ATP) is the most widely used carrier of free energy.



The phosphate groups store high free energy that can be used to drive many reactions.

ATP is synthesized by the glycolysis of sugars in the mitochondria

Recall that many reactions in biology require the synthesis of long polymeric molecules: DNA, RNA, proteins and polysaccharides. Each of these is free energetically unfavorable. In addition, each synthesis requires a **condensation reaction**:

$$XH + YOH \rightarrow XY + H_2O \quad \Delta G > 0$$

ATP readily enables this reaction through the following steps:

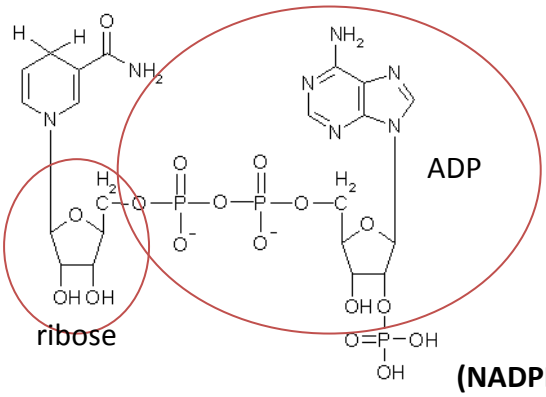
$$ATP + YOH \rightarrow YOPO_3 + ADP$$

$$XH + YOPO_3 \rightarrow XY + PO_4$$

where ADP is the diphosphate nucleotide and P is a phosphate group. Thus, by **dephosphorylation** ATP can drive condensation reactions.

NADH and NADPH – electron/proton carriers

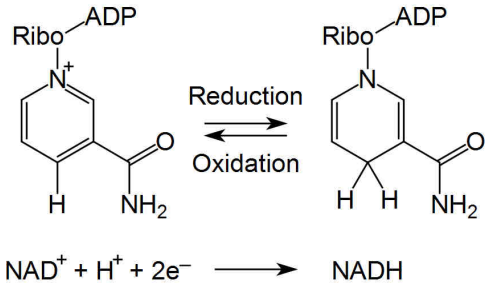
Another important class of carriers are **nicotinamide adenine dinucleotide (NAD+/NADH)** and **nicotinamide adenine dinucleotide phosphate (NADP+/NADPH).**



(NADPH)

The difference between the NAD and NADP versions is the presence of a phosphate group at the bottom right.

These molecules carry a proton and two electrons. They can convert between two forms, an **oxidized** form and a **reduced** form:



$\Delta G > 0$ for reduction, $\Delta G < 0$ for oxidation

Importantly, NADP and NADPH can facilitate reduction of other molecules by donating a proton to it:

$$C = C + NADPH + H^+ \rightarrow CH - CH + NADP^+$$

These molecules are very important in oxidation/reduction reactions inside the cell and are used extensively to synthesize other molecules

Why two molecules? Allows a division of labor and regulation since the additional phosphate group in NADPH can allow it to be recognized by different binding proteins and substrates than NADH:

- NADPH → works with enzymes to catalyze reactions that synthesize energy-rich biomolecules
- NADH → used in the generation of ATP from food molecules

Other carriers

There are a number of other energy carriers that perform more specific roles in biology. These are used to enable specific kinds of reactions beyond condensation and oxidation/reduction.