Lecture 28: Non-Equilibrium Thermodynamics & Pathway Flux

ΔG°, the standard energy, is the energy released when one mole of reactants are converted to one mole of products.

\[ \Delta G^o = \mu_b^{o} - \mu_a^{o} = -RT \ln K_{eq} = -RT \ln \frac{[B]_{eq}}{[A]_{eq}}. \]

It is defined by the equilibrium position of the reaction and it depends on the difference in the intrinsic energies of the two compounds:

- \( \mu_a^{o} \) = chemical energy of pure compound A
- \( \mu_b^{o} \) = chemical energy of pure compound B

The intrinsic energy is related to the electronic configuration. It is also the energy required to convert 1 mole of A to one mole of B.

ΔG° is insufficient to describe energy changes in metabolism because the concentrations of intermediates in a biochemical pathway are seldom at their equilibrium concentrations.

The Gibbs free energy, ΔG, is used to describe non-equilibrium conditions. It is the difference between the chemical potential of each compound (μ). For the reaction A ⇌ B:

\[ \Delta G = \mu_b - \mu_a = (\mu_b^{o} + RT \ln[B]) - (\mu_a^{o} + RT \ln[A]) \]

\[ \Delta G = \Delta G^o + RT \ln \frac{[B]}{[A]} \]

- ΔG indicates the spontaneous direction of the reaction.
- |ΔG| is the maximum energy released by the system as it approaches equilibrium. This energy can be captured to do work (or synthesize compounds).

ΔG = 0 the reaction is at equilibrium, the difference in the chemical potentials of A and B is zero, no energy can be gained converting A to B, or B to A.

ΔG < 0 The potential of A is larger than B, therefore A ⇌ B is spontaneous and |ΔG| amount of energy is released as it goes to equilibrium.

ΔG > 0 The potential of B is larger than A, the system will spontaneously move: B ⇌ A and |ΔG| of energy will be released as it goes to equilibrium.
Case 1: At equilibrium.
\[
\Delta G = (\mu^A - \mu^B) + RT \ln \left( \frac{[B]_{eq}}{[A]_{eq}} \right)
\]
\[
= (\mu^A - \mu^B) + RT \ln \left( \frac{[B]_{eq}}{[A]_{eq}} \right)
\]
\[
= \Delta G^0 + RT \ln \left( \frac{[B]_{eq}}{[A]_{eq}} \right)
\]
\[
= -RT \ln \left( \frac{[B]_{eq}}{[A]_{eq}} \right) = 0
\]

Case 2: [A] higher than its equilibrium point by \(\delta\).
\[
\Delta G = (\mu^A - \mu^B) + RT \ln \left( \frac{[B]_{eq}}{[A]_{eq}} \right) - RT \ln \left( \frac{[B]_{eq}}{[A]_{eq}} + \delta \right)
\]
\[
= (\mu^A - \mu^B) + RT \ln \left( \frac{[B]_{eq}}{[A]_{eq}} \right) - RT \ln \left( \frac{[B]_{eq}}{[A]_{eq}} + \delta \right)
\]
\[
= \Delta G^0 + RT \ln \left( \frac{[B]_{eq}}{[A]_{eq}} \right) - RT \ln \left( \frac{[B]_{eq}}{[A]_{eq}} + \delta \right)
\]
\[
= RT \ln \left( \frac{[B]_{eq}}{[A]_{eq}} \right) + \Delta G^0 - RT \ln \left( \frac{[B]_{eq} + \delta}{[A]_{eq}} \right)
\]

Case 3: [B] higher than its equilibrium point by \(\delta\).
\[
\Delta G = (\mu^A - \mu^B) + RT \ln \left( \frac{[B]_{eq}}{[A]_{eq}} \right) - RT \ln \left( \frac{[B]_{eq} + \delta}{[A]_{eq}} \right)
\]
\[
= (\mu^A - \mu^B) + RT \ln \left( \frac{[B]_{eq}}{[A]_{eq}} \right) - RT \ln \left( \frac{[B]_{eq} + \delta}{[A]_{eq}} \right)
\]
\[
= \Delta G^0 + RT \ln \left( \frac{[B]_{eq}}{[A]_{eq}} \right) - RT \ln \left( \frac{[B]_{eq} + \delta}{[A]_{eq}} \right)
\]
\[
= RT \ln \left( \frac{[B]_{eq}}{[A]_{eq}} \right) + \Delta G^0 - RT \ln \left( \frac{[B]_{eq} + \delta}{[A]_{eq}} \right)
\]

Both \(\ln\) terms are \(<0\), therefore \(\Delta G\) is \(<0\).
Both \(\ln\) terms are \(>0\), therefore \(\Delta G\) is \(>0\).

4. Flux and Coupling of Reactions: A key feature of all biochemical pathways is that there is a constant flux of material through the pathway. To insure a constant flux through the pathway it is necessary to insure that the Gibbs energy of the products are lower in energy than the substrates, such that the natural flow is always from substrates to products in each step of the pathway.

**Direct Coupling:** Many steps in biochemical pathways involve reactions that are extremely unfavorable, i.e. a large positive \(\Delta G^0\). This energy barrier reduced by the direct coupling of the unfavorable reaction to a favorable one, with both reactions occurring at the same time in the active site of one enzyme. The energetics of each reaction are most easily seen by considering the half-reactions.

For example, the first reaction in glycolysis, catalyzed by the enzyme hexose kinase, converts glucose to glucose-6-phosphate. The high energy of ATP is used to drive this unfavorable reaction by direct coupling — the phosphate group is transferred directly from ATP to glucose.

**Indirect Coupling:** By lowering the concentration of the product below its equilibrium position, a reaction can be made spontaneous; the \(\Delta G\) becomes \(<0\). This generally implies that a reaction further down the pathway has a large negative \(\Delta G^0\), such that the last compound in the pathway is kept below equilibrium concentration.

**Example of Indirect Coupling:** For the pathway \(A \rightarrow B\),

- Concentration of [A] is \(10^{-5}\) M under normal metabolic conditions. This would give an equilibrium concentration of [B]eq = \(10^{-5}\) M (i.e. [A] > [B] at equilibrium).
- Standard free energy, \(\Delta G^0\), of the first reaction \((A \rightarrow B)\) is +5.75 kJ/mol.

1. What is the direction of the reaction if the concentration of [B] is \(10^{-5}\) M? \(A \rightarrow B\)

2. Why is this reaction now spontaneous in the forward direction, even though the equilibrium favors [A]?