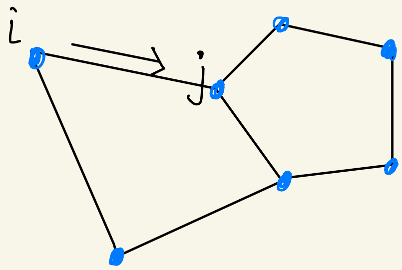
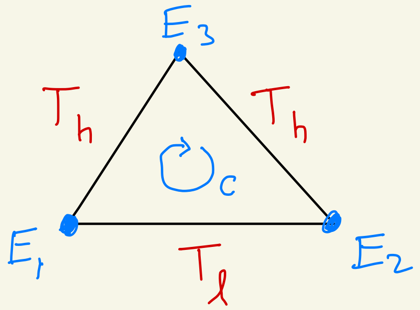
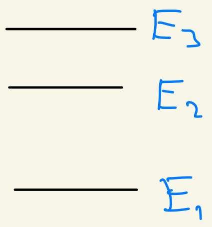
From last class:

$$\boxed{\delta S_r(i\to j) = \ln \frac{R_{ji}}{R_{ij}}}$$



Example 1.





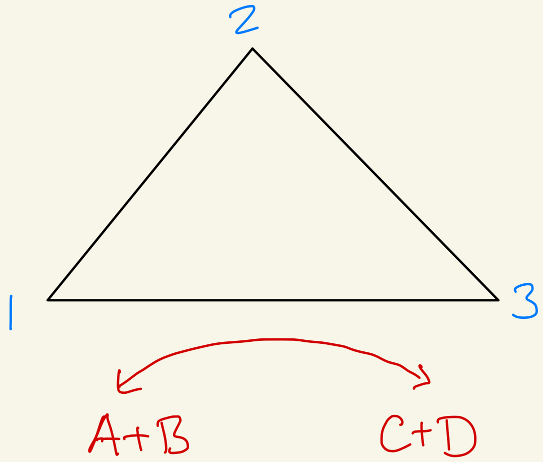
$$A_c = \ln\left(\frac{R_{12}}{R_{21}}\cdot\frac{R_{23}}{R_{32}}\cdot\frac{R_{31}}{R_{13}}\right) = \underbrace{(E_2-E_1)\cdot\left(\frac{1}{T_\ell}-\frac{1}{T_h}\right)}_{\Delta S_r} > 0$$

Physically, when the system evolves once around the cycle c, an amount of energy $E_2 - E_1$ is transferred from the hot reservoir (T_h) to the cold reservoir (T_ℓ).

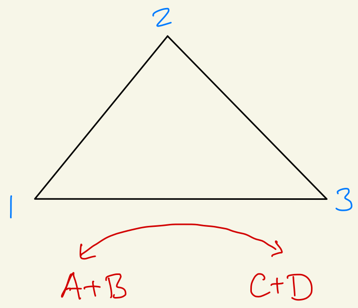
Example 2.

Consider a single molecule (system, S) immersed in an aqueous solution (H_2O) contained other molecules of types A, B, C, & D. S has 3 states.

Assume $N_A, N_B, N_C, N_D \gg 1$ (but $N_S = 1$).



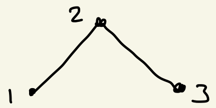
S can make transitions $1 \longleftrightarrow 2$ & $2 \longleftrightarrow 3$ due to thermal fluctuations, but it can proceed $1 \to 3$ only by catalyzing the reaction $A+B \to C+D$, & it can proceed from 3 to 1 only by catalyzing $C+D \to A+B$.



The transitions $1 \leftrightarrow 2$ & $2 \leftrightarrow 3$ satisfy det. balance:

$$\frac{R_{12}}{R_{21}} = e^{-\beta(E_1-E_2)} , \quad \frac{R_{23}}{R_{32}} = e^{-\beta(E_2-E_3)}$$

(Thus if there were no A, B, C, D in the solution, we would have a tree graph

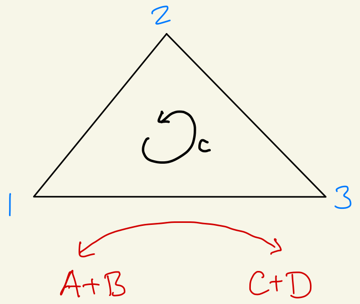


& S would relax to an equil. state described by the Boltzmann distrib'n.)

What about R_{13} & R_{31}?

Let's write $\frac{R_{31}}{R_{13}} = e^{-\beta(E_3-E_1)+\beta X}$

The quantity X measures the deviation away from detailed balance.



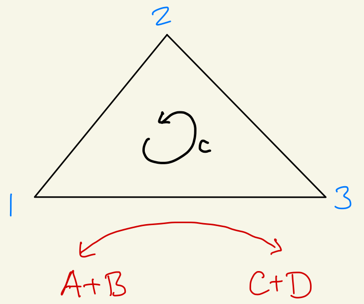
$$\frac{R_{12}}{R_{21}} = e^{-\beta(E_1 - E_2)}$$

$$\frac{R_{23}}{R_{32}} = e^{-\beta(E_2 - E_3)}$$

$$\frac{R_{31}}{R_{13}} = e^{-\beta(E_3 - E_1) + \beta X}$$

- If $X=0$ then det. balance is satisfied $\left(\frac{R_{12}}{R_{21}} \cdot \frac{R_{23}}{R_{32}} \cdot \frac{R_{31}}{R_{13}} = 1 \right)$ & the stationary state $\vec{\pi}$ is an equilibrium state $(\pi_i \propto e^{-\beta E_i})$ w/ $J^s = 0$.
- If $X>0$ then transitions $1 \to 3$ are enhanced, relative to $3 \to 1$, hence we expect $J^s > 0$ (CCW).
- If $X<0$ then transitions $3 \to 1$ are enhanced & we expect $J^s < 0$ (CW).

We refer to X as a <u>thermodynamic force</u>. Such forces arise when the surroundings are not in equil. In Example 1, the 2 thermal reservoirs were not in equilibrium $(T_l < T_h)$. Let's see how things work out in Example 2.



$$\frac{R_{12}}{R_{21}} = e^{-\beta(E_1 - E_2)}$$

$$\frac{R_{23}}{R_{32}} = e^{-\beta(E_2 - E_3)}$$

$$\frac{R_{31}}{R_{13}} = e^{-\beta(E_3 - E_1) + \beta X}$$

In this case, let's solve for X by analyzing the entropy produced in the surroundings when the system evolves thru one cycle $(1 \to 3 \to 2 \to 1)$, & then using $\Delta S_r(1\to3\to2\to1) = \ln\left(\frac{R_{31}}{R_{13}} \cdot \frac{R_{23}}{R_{32}} \cdot \frac{R_{12}}{R_{21}}\right) \equiv A_c$

$3 \to 2$: $\Delta E = E_2 - E_3$; $\Delta E_r = -\Delta E$; $\delta S_r = \beta(E_3 - E_2)$

$2 \to 1$: $\delta S_r = \beta(E_2 - E_1)$

$1 \to 3$: $A + B \to C + D$; $\frac{\partial S}{\partial N_i} = -\beta \mu_i$

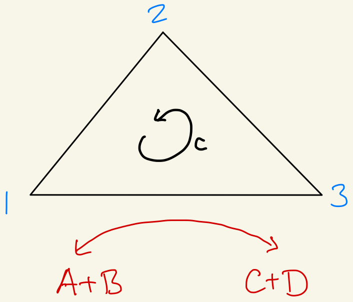
$$\to \delta S_r = \beta(\mu_A + \mu_B - \mu_C - \mu_D + E_1 - E_3)$$

$$\therefore \quad \Delta S_r(1\to3\to2\to1) = \beta(\mu_A + \mu_B - \mu_C - \mu_D) = -\beta \cdot \Delta G_{rxn}$$

$$A_c = \ln\left(\frac{R_{31}}{R_{13}} \cdot \frac{R_{23}}{R_{32}} \cdot \frac{R_{12}}{R_{21}}\right) = \beta X$$

Conclude: $\boxed{X = -\Delta G_{rxn}(A + B \to C + D)}$

The thermo. force X is positive when $\mu_A + \mu_B > \mu_C + \mu_D$, i.e. when the rxn is "downhill" in G.



$$X = -\Delta G_{rxn}(A+B \to C+D)$$
$$= \mu_A + \mu_B - \mu_C - \mu_D$$
$$A_c = \beta X = -\beta \Delta G_{rxn}$$

Think about it this way ...

Every time S proceeds thru the cycle $c = 1 \to 3 \to 2 \to 1$, it catalyzes the conversion of one A & one B molecule into one C & one D molecule.

If $\Delta G_{rxn}(A+B \to C+D) < 0$, then this conversion increases the entropy of the Universe, hence it is favored. The disequilibrium of the surrounding solution thus applies a CCW force $X > 0$, which produces a CCW current $J^S > 0$, which in turn increases the entropy of the solution.

As long as $\Delta G_{rxn} < 0$ there is a surplus of A's & B's, & a deficit of C's & D's. By catalyzing the rxn, the system S is helping to bring the solution toward equilibrium.

To this point, I've obtained the result

$$A_c = -\beta \underbrace{\Delta G_{rxn}}_{\mu_C+\mu_D-\mu_B-\mu_A}$$

$$\ln\left(\frac{R_{31}}{R_{13}}\cdot\frac{R_{23}}{R_{32}}\cdot\frac{R_{12}}{R_{21}}\right)$$

by appealing to the claim $\delta S_r(i\to j) = \ln \frac{R_{ji}}{R_{ij}}$.

Now let's see how the same result for A_c can be motivated by appeal to standard chemical kinetics.

Imagine observing the evolution of S for a long time:

$$\cdots\ 1\,3\,1\,2\,\overbrace{1\,3\,2\,1}^{+}\,2\,\underbrace{1\,2\,3}_{-}\,\overbrace{1\,2\,3\,1}^{-}\,3\,\underbrace{1\,3\,2}_{+}\,\overbrace{1\,2\,3\,2\,3\,1}^{-}\ \cdots$$

Each CCW cycle (+) ⟷ $A+B \longrightarrow C+D$

Each CW cycle (−) ⟷ $A+B \longleftarrow C+D$

$R_+ \equiv$ avg. rate of CCW cycles
$R_- \equiv$ avg. rate of CW cycles
} in stationary state

$$\frac{R_+}{R_-} = \frac{R_{31}R_{23}R_{12}}{R_{13}R_{32}R_{21}}$$

← product of CCW R_{ij}'s
← product of CW R_{ij}'s

(proof left as exercise)

$$\therefore \quad \ln\frac{R_+}{R_-} = A_c$$

Now analyze R_+/R_- using chemical kinetics (Law of Mass Action):

$$A + B \underset{k_-[C][D]}{\overset{k_+[A][B]}{\rightleftharpoons}} C + D \qquad \text{(assuming dilute soln)}$$

$[A]$ = concentration of A molecules, etc.

$k_\pm$ = rate constants

In equilibrium the net rates are equal:

$$k_+ [A]^{eq} [B]^{eq} = k_- [C]^{eq} [D]^{eq}$$

We also have (dilute sol'n):

$$\mu_A = \mu_A^0 + \beta^{-1} \ln [A] \quad , \text{etc.}$$

↳ standard state chem. potential $(1 \frac{mol}{L})$

Therefore in equil. we have

$$k_+ e^{\beta(\mu_A^{eq} - \mu_A^0)} e^{\beta(\mu_B^{eq} - \mu_B^0)} = k_- e^{\beta(\mu_C^{eq} - \mu_C^0)} e^{\beta(\mu_D^{eq} - \mu_D^0)}$$

But $\mu_A^{eq} + \mu_B^{eq} = \mu_C^{eq} + \mu_D^{eq}$, $\therefore$

$$\frac{k_+}{k_-} = e^{-\beta(\mu_C^0 + \mu_D^0 - \mu_A^0 - \mu_B^0)} = e^{-\beta \Delta G^0_{rxn}}$$

ΔG^0_{rxn} = Gibbs free energy of rxn when all species (A–D) are in standard state.

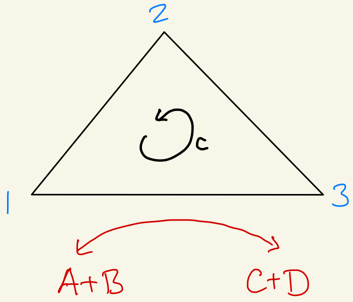
Returning to the case of arbitrary concentrations
(not necessarily equil., not necessarily stand. state,
but still dilute!):

$$R_+ = k_+ [A][B] = k_+ e^{\beta(\mu_A - \mu_A^0)} e^{\beta(\mu_B - \mu_B^0)}$$

$$R_- = k_- [C][D] = k_- e^{\beta(\mu_C - \mu_C^0)} e^{\beta(\mu_D - \mu_D^0)}$$

$$A_c = \ln \frac{R_+}{R_-} = \underbrace{\ln \frac{k_+}{k_-} + \beta (G^0_{rxn}}_{\text{these cancel (see prev. slide)}} - \Delta G_{rxn}) = -\beta \Delta G_{rxn}$$

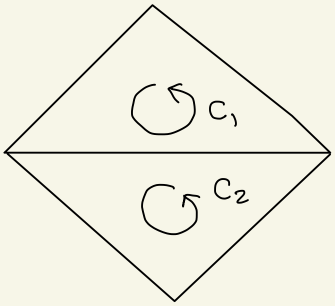
$$\boxed{\underbrace{A_c}_{\text{affinity}} = \beta \underbrace{X}_{\text{thermo. force}} = -\beta \underbrace{\Delta G_{rxn}}_{\text{Gibbs free energy of rxn}}}$$



In this example, only transitions along the edge 1-3 were coupled to the chem. rxn, whereas the other transitions (1-2, 2-3) were driven solely by thermal fluctuations.

In more complicated situations, multiple edges might be coupled to rxns, and there might be competition among them. For any cycle c in the graph, the affinity A_c is the net thermodynamic force that drives the system around that cycle.

Example

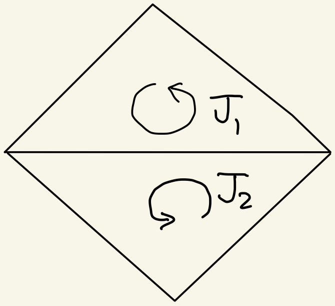


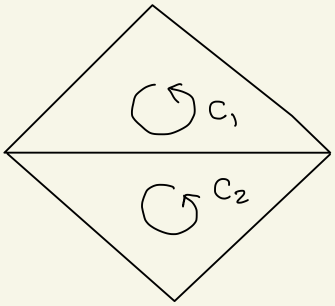
Suppose $A_{c_1} > 0$, $A_{c_2} = 0$
Then we'll get CCW current around c_1, which induces CCW (positive) current around c_2:

Exercise: show this

$A_{c_1} > 0$

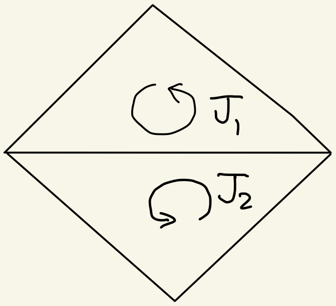
$A_{c_2} = 0$





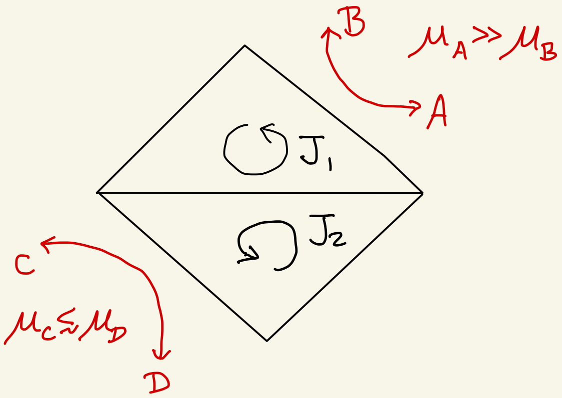
$A_{c_1} > 0$

$A_{c_2} = 0$



Now imagine we turn on a weak affinity $A_{c_2} < 0$. This thermodynamic force opposes the CCW current J_2 but doesn't change its sign (for sufficiently small $|A_{c_2}|$.)

Thus the strong affinity A_{c_1} generates current around c_2 that flows contrary to the weak affinity around that cycle.



Net effect:

The "downhill" rxn $A \to B$ drives the "uphill" rxn $C \to D$.

This situation – a competition between thermo. forces in which one prevails over the other – is called free energy transduction.

This is at the heart of many molecular machines / motor proteins.
E.g. F0-F1 ATP synthase, found in our mitochondria...

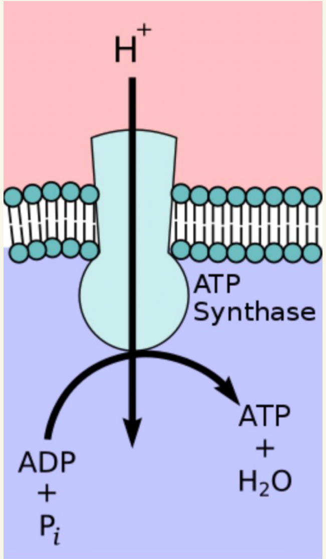
References:

- T.L. Hill, Free Energy Transduction and Biochemical Cycle Kinetics (1989)

- Lipowsky & Leipelt,
  "Chemomechanical Coupling of Molecular Motors: Thermodynamics, Network Representations, & Balance Conditions"
  J. Stat. Phys. (2008) – course website

$\mu_{ATP} + \mu_{H_2O}$
$> \mu_{ADP} + \mu_{P_i}$

ATP hydrolysis:
$ATP + H_2O$
$\rightarrow ADP + P_i$



$\leftarrow$ high μ_{H^+} outside

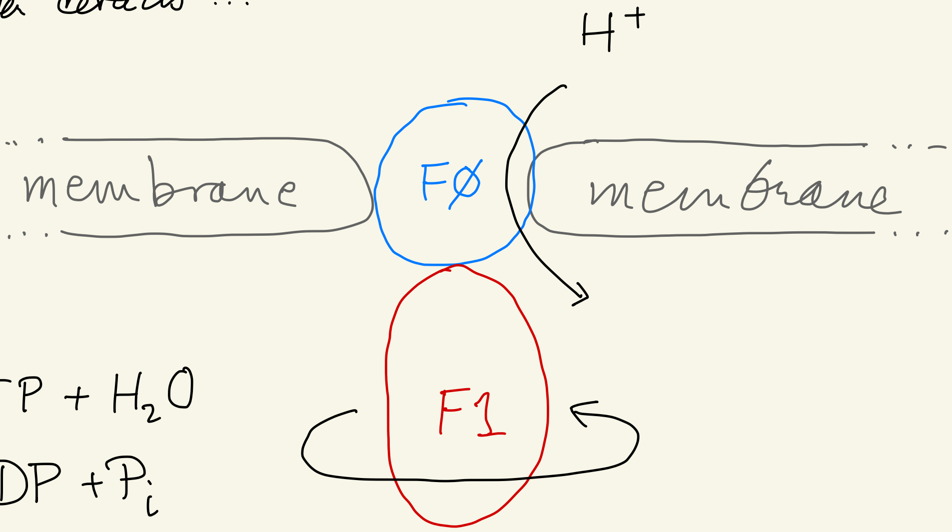
$\leftarrow$ low μ_{H^+} inside

The F0–F1 ATP synthase has evolved so that the flow of protons from outside to inside is opposed by the hydrolysis of ATP. Specifically, it catalyzes the rxn

$$ADP + P_i + 3H^+_{out} \rightleftharpoons ATP + H_2O + 3H^+_{in}$$

The proton gradient across the membrane provides a thermo. force in the "forward" direction, while the high chem. pot. of ATP is a thermo. force in the "backward" direction. In the mitochondria, the proton gradient wins the competition.

Further details ...



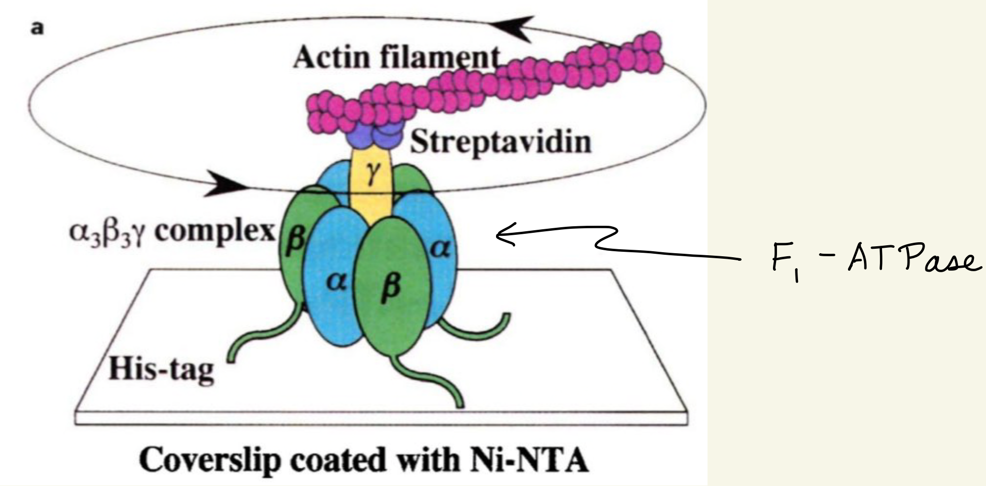
$ATP + H_2O$
$\rightarrow ADP + P_i$

Proton flow out → in drives the mechanical rotation of F1 with respect to F0 in one direction, & ATP hydrolysis drives it in the other direction. "Mechanochemistry."
Since the proton gradient wins, ATP molecules are produced.

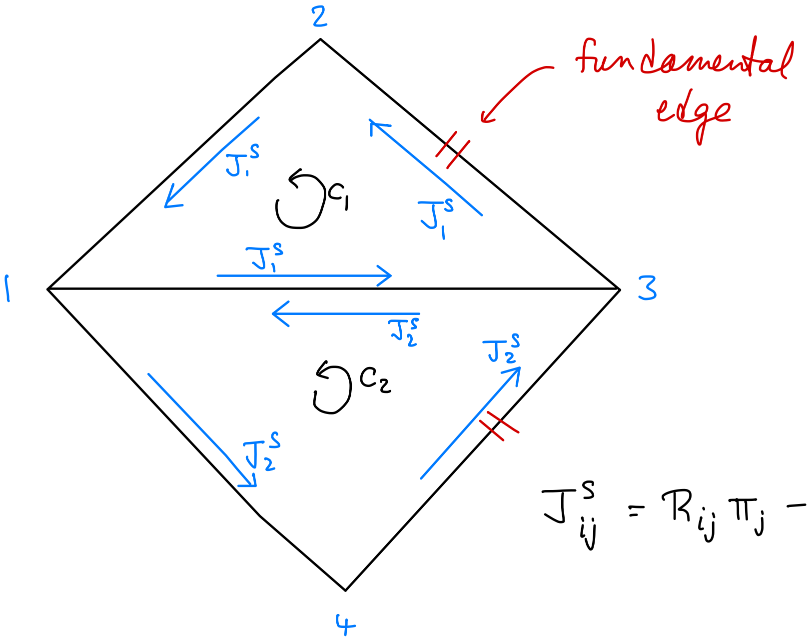
Experiments: (Kinosita lab)

Noji et al, 1997 –
Direct observation of rotation of F_1-ATPase

Itoh et al, 2004 –
Mechanically driven ATP synthesis
by F_1-ATPase



Cycle decomposition & steady states.



$$J^s_{ij} = R_{ij}\pi_j - R_{ji}\pi_i$$

$$\begin{cases} J^s_1 = \text{current thru fundamental edge of cycle 1} = J^s_{23} = \text{current through cycle 1} \\ J^s_2 = J^s_{34} \end{cases}$$

From these currents we can construct the steady state current along any edge. (illustrated)

e.g. $J^s(2\to 1) = J^s_1$, $J^s(1\to 3) = J^s_1 - J^s_2$, etc.

Also: $\boxed{\dot{S}^s_{tot} = \sum_{cycles} A_c J^s_c \geq 0}$ (Schnakenberg 1976)