Lecture 6.
Preliminary and simple applications of statistical mechanics

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Main contents

- Fundamental concepts and equations
- Non-interaction ideal models
- Simple models of ligand-receptor binding and gene expression
- Law of mass action
- Discussions on irreversible process
§6.1 Fundamental concepts & equations
Conventional thermodynamics

- **Object**
  - Systems: large number of particles (~$10^{23}$)
  - Short-range interaction between particles (ideal gas, vdW gas, plasma, polymer; gravity system, + or - charged system)
  
  Interaction potential $\downarrow< r^{-3}$ for $r \to \infty$

- An isolated system can reach thermal equilibrium through long enough but finite-time relaxation
• Four thermodynamic laws
  – 0th: it is possible to build a thermometer
  – 1st: energy is conserved \[ dU = \delta Q + \delta W \]
  – 2nd: not all heat can be converted into work \[ TdS \geq \delta Q \]
  – 3rd: 0K cannot be reached via a finite reversible steps

Note in thermodynamics:

(1) temperature, similar to mass, is an operational definition (操作性定义)

(2) entropy can be defined as \[ dS = \frac{\delta Q}{T} \] via reversible process
• Free energy (Helmholtz)

\[ F = U - TS \]

1st+2nd+const. T:

\[ dF = dU - TdS = \overline{d} \, W_k + \overline{d} \, Q - TdS \leq \overline{d} \, W_k \]

\[ -\overline{d} \, W_k \leq -d \, F \]

Free energy change = maximum work done by the system on the outer environment in isothermal process
Statistical mechanics

- Function

A *bridge* from *microscopic motions* of a large number of molecules to *macroscopic behavior* of the system consisting of these molecules.
- **Macrostate**: thermodynamic EQ state
  - e.g. PVT, HMT etc.
- **Microstate**: phase point \((q,p)\)

Each macrostate corresponds to many microstates!
Each microstate occurs at some probability.

Task of stat. mech. is to find this probability distribution and then explain further the macroscopic quantities!
• Statistical Postulate (统计假说)
  - When an isolated system is left alone long enough time, it evolves to thermal equilibrium.
  - Equilibrium is not one microstate, but rather that probability distribution of microstates having the greatest possible disorder allowed by the physical constraints on the system.

**Key question:** How to measure disorder?
A good quantity ($I$) to measure disorder satisfies

- **Continuity**: continuous respect to $P_1, P_2, \ldots, P_M$
- **Zero for pure state**: $I=0$ for $P_1 = 1$ and others=0
- **Maximum for most mixed state**: $\max I$ for $P_j = 1/M$
- **Additivity**: $I(X+Y) = I(X) + I(Y)$ for independent $X$ and $Y$
Shannon's information entropy (1948)

\[ I = -K \sum_{j=1}^{M} P_j \ln P_j \quad ; \quad K > 0 \]

Problem: prove that \( I_{\text{max}} = K \ln M \) if and only if \( P_j = 1/M \).

(1) constraint: \( \sum_{j=1}^{M} P_j = 1 \)

(2) Lagrange problem:

\[ \tilde{I} \equiv I - \lambda \left( \sum_{j=1}^{M} P_j - 1 \right) \]

\[ \frac{\partial \tilde{I}}{\partial P_j} = 0 \Rightarrow P_j = e^{- (1 + \lambda/K)} \quad \text{(const.)} \]

\[ \frac{\partial \tilde{I}}{\partial \lambda} = 0 \Rightarrow \sum_{j=1}^{M} P_j = 1 \quad \rightarrow \quad P_j = 1/M \]

(3) Max. or Min. ?:

\[ \frac{\partial^2 \tilde{I}}{\partial P_j \partial P_k} \bigg|_{P_j=1/M} = -KM \delta_{jk} \quad \Rightarrow \text{maximum!} \]
Boltzmann Entropy

• Equilibrium of isolated system: const. $E, N, V$

$W(E,N,V)$: the number of allowed microstates

Measure of disorder: $I = -K \sum_{j=1}^{W} P_j \ln P_j$

Constraint: $\sum_{j=1}^{W} P_j = 1$

Each microstate is equally probable! $I = I_{max}$

$S \equiv \frac{k_B}{K} \ln W$ (Boltzmann entropy)

Boltzmann Entropy = constant X maximal value of disorder
• **Canonical system**: A system in equilibrium state at constant \( N, V \) & \(<E>\)

Allowed microsates: \( \Gamma_j \equiv \{(r_1, p_1; r_2, p_2; \cdots; r_N, p_N)\}_j \)

with energy \( E_j; j=1,2,\cdots \)  

Probability: \( P_j \equiv P(E_j) \)

Measure of disorder: \( I = -K \sum_j P_j \ln P_j \)

Constraints: \( \sum_j P_j = 1 \) \( \sum_j P_j E_j = \text{const.} \)

**Problem**: prove that \( \max \{I/K\} \) with the above constraints gives

\[
P_j = \frac{e^{-\beta E_j}}{Z}
\]

---Boltzmann distribution

where \( \beta \) is a constant and \( Z = \sum_j e^{-\beta E_j} \) ---Partition function
Problem: if we interpret $\langle E \rangle = U$, what's the physical meaning of $\beta$?

$$P_j = e^{-\beta E_j} / Z \Rightarrow U = \langle E \rangle = \sum_j E_j e^{-\beta E_j} / Z$$

$$S \equiv \frac{k_B}{K} I_{max} = -k_B \sum_j P_j \ln P_j = -k_B \sum_j \frac{e^{-\beta E_j}}{Z} \ln \left( \frac{e^{-\beta E_j}}{Z} \right)$$

$$= -k_B \sum_j \frac{e^{-\beta E_j}}{Z} (-\beta E_j - \ln Z) = k_B \beta U + k_B \ln Z$$

For constant $N, V$

$$\frac{\partial U}{\partial \beta} = U^2 - \langle E^2 \rangle$$

$$\frac{\partial S}{\partial \beta} = k_B \beta [U^2 - \langle E^2 \rangle]$$

Thermodynamic relation in isochoric (等容) reversal process

$$dU = T \, dS \Rightarrow \frac{\partial S}{\partial U} \bigg|_{N,V} = \frac{1}{T}$$

$$\beta = 1 / k_B T$$


We can define

$$
\frac{1}{T} = \frac{\partial S}{\partial U} \bigg|_{N,V}
$$

Then Stat. Mech. & thermodynamics are consistent.

\[ P_j = e^{-\beta E_j} / Z \]
\[ Z = \sum_j e^{-\beta E_j} \]
\[ \beta = 1 / k_B T \]

\[ U = \langle E \rangle = \sum_j E_j e^{-\beta E_j} / Z \]

\[ S \equiv \frac{k_B}{K} I_{\text{max}} = k_B \beta U + k_B \ln Z \]

**Problem:** prove that

\[ F = -k_B T \ln Z \]

**Problem:** prove that

\[ U = -\frac{\partial \ln Z}{\partial \beta} \]
Macrostate & microstate are relative

- One person’s macrostate is another’s microstate

<table>
<thead>
<tr>
<th>STATE</th>
<th>WEIGHT</th>
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<tbody>
<tr>
<td>$X_1$ 1</td>
<td>$e^{-\beta \epsilon_1}$</td>
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<tr>
<td>$X_1$ 2</td>
<td>$e^{-\beta \epsilon_2}$</td>
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<td>$X_1$ 3</td>
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<tr>
<td>$X_1$ $n_1$</td>
<td>$e^{-\beta \epsilon_{n_1}}$</td>
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<td>$X_2$ $n_1+1$</td>
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\[
p(X_1) = \sum_{m=1}^{n_1} p_m = \frac{1}{Z} \sum_{m=1}^{n_1} e^{-\beta \epsilon_m} = \frac{1}{Z} e^{-\beta G(X_1)}
\]

\[
Z_1
\]

\[
G(X_1) = -k_B T \ln Z_1
\]
§6.2 Non-interaction ideal models
Ideal gas

- Law of ideal gas

\[ P = n k_B T \]

Note: here \( P \) is the pressure!

Problem: please check the dimension!

- The origin of \( P \)

\[
\Delta t = \frac{2L}{v_x} \quad \text{(a round trip)}
\]

\[
f_1 = 2 \frac{mv_x}{\Delta t} = m v_x^2 / L
\]

\[
p_1 = f_1 / L^2 = m v_x^2 / L^3
\]

\[
P = \langle \sum p_1 \rangle = \sum \langle p_1 \rangle = \left( \frac{N}{L^3} \right) m \langle v_x^2 \rangle = n m \langle v_x^2 \rangle
\]
Interpretation of temperature

\[ P = n k_B T \]
\[ P = n m \langle v_x^2 \rangle \]
\[ \Rightarrow \frac{1}{2} m \langle v_x^2 \rangle = \frac{1}{2} k_B T = \frac{1}{2} m \langle v_y^2 \rangle = \frac{1}{2} m \langle v_z^2 \rangle \]

The average energy per DOF is \( k_B T/2 \).

\[ v^2 = v_x^2 + v_y^2 + v_z^2 \Rightarrow \frac{1}{2} m \langle v^2 \rangle = \frac{3}{2} k_B T \]

\( \langle E \rangle \) of each molecule \((3/2)k_B T!\)

Problem: prove that

\[ \sqrt{\langle v^2 \rangle} \approx 500 \text{ m/s} \quad \text{for air molecules at room temperature} \]
• Maxwell distribution of molecular velocities

\[
\frac{dN(v_x, v_y, v_z)}{N} \equiv p(v_x, v_y, v_z) \, dv_x \, dv_y \, dv_z
\]

Distribution function

Maxwell distribution

\[
p(v_x, v_y, v_z) = A \, e^{-mv^2/2k_BT}
\]

\[v^2 = v_x^2 + v_y^2 + v_z^2\]

Problem: find A?

\[
\int_{-\infty}^{\infty} dv_x \int_{-\infty}^{\infty} dv_y \int_{-\infty}^{\infty} dv_z \, p(v_x, v_y, v_z) = 1 \Rightarrow A = \left( \frac{m}{2\pi k_B T} \right)^{3/2}
\]

Problem: please confirm that \(<E_K>\) of each molecule \((3/2)k_B T\)
The proportional number of molecules with velocities between \( u \) and \( u + du \)

\[
N \equiv \frac{dN(u)}{N} = p(u) du = \sum p(v_x, v_y, v_z) dv_x dv_y dv_z
\]

\[
= \left( \frac{m}{2 \pi k_B T} \right)^{3/2} e^{-mu^2/2k_BT} \times 4\pi u^2 du
\]

\[
p(u) = \left( \frac{2}{\pi} \right)^{1/2} \left( \frac{m}{k_B T} \right)^{3/2} u^2 e^{-mu^2/2k_BT}
\]

Question: what will happen when \( T \to 0 \)?

Problem: please prove

\[
p(E_K) \propto \sqrt{E_K} e^{-E_K/k_BT}
\]
Chemical reaction

- Reaction coordinate & activation barrier

Reaction coordinate (反应坐标): the fast reaction path from reactant to resultant in the configuration space.

\[ \Delta E_a \] : activation energy

Potential curve along the reaction coordinate
Intuitively, the molecules of reactant with $E_K \geq \Delta E_a$ can escape from the barrier. Thus the reaction rate

$$r \propto \frac{dN \left( E_K \geq \Delta E_a \right)}{N}$$
Problem: please prove

\[
\frac{dN \left( E_K \geq \Delta E_a \right)}{N} = e^{-\Delta E_a/k_B T}
\]

\[
dN(E_K \geq \Delta E_a) = \text{number of molecules outside the ellipse}
\]

\[
p(v_1, v_2) \, dv_1 \, dv_2 \propto e^{-\frac{(m_1 v_1^2 + m_2 v_2^2)}{2 k_B T}} \, dv_1 \, dv_2
\]

\[
p(V_1, V_2) \, dV_1 \, dV_2 \propto e^{-\frac{m(V_1^2 + V_2^2)}{2 k_B T}} \, dV_1 \, dV_2
\]

\[
p(V) \, dV \propto V \, e^{-\frac{mV^2}{2 k_B T}} \, dV
\]

\[
\frac{dN \left( E_K \geq \Delta E_a \right)}{N} = \int_{\sqrt{2\Delta E_a/m}}^{\infty} p(V) \, dV = e^{-\Delta E_a/k_B T}
\]

\[
\int_0^\infty p(V) \, dV
\]

Hard Question: What is missed in our discussion?

Arrhenius rate law

\[
r \propto e^{-\Delta E_a / k_B T}
\]
- How to increase the reaction rate?

\[ r = r_0 e^{-\frac{\Delta E_a}{k_B T}} \]

Arrhenius rate law

Two ways to increase the reaction rate:
(1) increase temperature (heat)
(2) decrease the activation barrier (enzyme)
• *$S$ of Ideal gas* at constant $E, N, V$

\[
E = \sum_{i=1}^{N} \frac{m}{2} v_i^2 = \frac{m}{2} \sum_{i=1}^{N} v_i^2 \equiv \frac{m}{2} u^2 \quad u \text{ is a } 3N\text{-dimensional vector}
\]

\[
|u| = \sqrt{\frac{2E}{m}} \quad u \text{ is located in } (3N-1)\text{-dimensional sphere with radius } (2E/m)^{1/2}
\]

For $N$ molecules at fixed positions, each vector $u$ can be reached

\[
W(E, N, V) \propto \text{surface of the sphere } \propto \left(\sqrt{\frac{2E}{m}}\right)^{3N-1}
\]

Each particle can stay any place in position space

\[
W(E, N, V) = C \times V^N E^{3N/2} \quad \text{(for large } N\text{)}
\]

\[
S = k_B \ln W(E, N, V) = k_B \left( \ln C + N \ln V + \frac{3N}{2} \ln E \right)
\]

**Question:** please find the dimension of constant $C$. 
• \( U, S, F \) of a box of ideal gas at constant \( N, V \)

\[
E = \sum_{i=1}^{N} \frac{p_i^2}{2m}
\]

\[
Z = \frac{1}{N!} \int e^{-\beta \sum_i p_i^2/2m} \prod_i \frac{d^3 r_i d^3 p_i}{\hbar^3}
\]

Why is there \( N! \) ?

\[
Z = \frac{V^N}{N!} \left( \frac{2\pi m}{h^2 \beta} \right)^{3N/2}
\]

\[
\ln Z = \ln \left[ \frac{V^N}{N!} \left( \frac{2\pi m}{h^2 \beta} \right)^{3N/2} \right] - \frac{3N}{2} \ln \beta
\]

\[
U = -\frac{\partial \ln Z}{\partial \beta} = \frac{3N}{2\beta} = \frac{3N k_B T}{2} \quad \Rightarrow \frac{U}{N} = \frac{3 k_B T}{2}
\]
\[ F = -k_B T \ln Z = -k_B T \ln \left[ \frac{N^N}{N!} \left( \frac{2\pi m}{h^2} \beta \right)^{3N/2} \right] = -Nk_B T \left[ 1 + \ln \frac{V}{N} \left( \frac{2\pi m}{h^2} \right)^{3/2} \right] \]

\[ = -Nk_B T \left[ 1 + \ln \frac{V}{N} \left( \frac{2\pi mk_B T}{h^2} \right)^{3/2} \right] \Rightarrow S = \frac{U - F}{T} = Nk_B \left[ \frac{5}{2} + \ln \frac{V}{N} \left( \frac{2\pi mk_B T}{h^2} \right)^{3/2} \right] \]

**Problem:** what's \( \Delta S \) if \( V \rightarrow 2V \)?

\[ \Delta S = Nk_B \ln 2 \]

**Problem:** find the entropy density for (dilute) ideal gas

\[ c_* = \left( \frac{2\pi mk_B T}{h^2} \right)^{3/2} \approx 10^{32} \text{ m}^{-3} \quad \text{For} \quad c = \frac{N}{V} \ll c_* , \quad \frac{S}{V} = -k_B c \ln \frac{c}{c_*} \]
Dilute Solutions

- Free energy of solution & solute chemical potential

\[ S_{mix} = k_B \ln \left( \frac{(N_{H_2O} + N_s)!}{N_{H_2O}!N_s!} \right) \approx -k_B \left[ N_{H_2O} \ln \frac{N_{H_2O}}{N_{H_2O} + N_s} + N_s \ln \frac{N_s}{N_{H_2O} + N_s} \right] \]

Stirling approx.

Total lattice: \( N_s + N_{H_2O} \)

Total states:

\[ W = \frac{(N_{H_2O} + N_s)!}{N_{H_2O}!N_s!} \]
dilute solution $\Rightarrow \frac{N_s}{N_{H_2O}} \ll 1 \Rightarrow S_{mix} \approx -k_B \left( N_s \ln \frac{N_s}{N_{H_2O}} - N_s \right)$

$\Rightarrow G_{tot}(T, p, N_{H_2O}, N_s) = N_{H_2O} \mu_0^0(T, p) + N_s \varepsilon_s(T, p) + k_B T \left( N_s \ln \frac{N_s}{N_{H_2O}} - N_s \right)$

$\Rightarrow \mu_s = \left( \frac{\partial G_{tot}}{\partial N_s} \right)_{T, p} = \varepsilon_s + k_B T \ln \frac{c}{c_0}$

with $c = \frac{N_s}{V_{tot}}$, $c_0 = \frac{N_{H_2O}}{V_{tot}}$

**Problem**: please prove that the chemical potential of ideal gas has the similar form.

**Homework**: please prove that the chemical potential for non-interaction system of multi-components is

$$
\mu_i = \mu_{i0} + k_B T \ln \frac{c_i}{c_{i0}}
$$

$c_{i0} = 1 \text{ M} \quad \text{---reference state}$

$$
\mu_{i0} = \varepsilon_{is} + k_B T \ln \frac{c_{i0}}{c_0}
$$
- **Osmotic pressure**

  Permeability of the membrane to water

  Equilibrium state \( \mu_{H_2O}^L = \mu_{H_2O}^R, T_L = T_R = T \)

  Chemical potential of water

  \[
  G_{tot}(T, p, N_{H_2O}, N_s) = N_{H_2O} \mu_{H_2O}^0(T, p) + N_s c_s(T, p) + k_B T \left( N_s \ln \frac{N_s}{N_{H_2O}} - N_s \right)
  \]

  \[
  \mu_{H_2O}(T, p) = \left( \frac{\partial G_{tot}}{\partial N_{H_2O}} \right)_{T, p} = \mu_{H_2O}^0(T, p) - \frac{N_s}{N_{H_2O}} k_B T
  \]

  Van't Hoff formula

  \[
  \begin{cases}
  \mu_{H_2O}^L = \mu_{H_2O}^0(T, p_L) \\
  \mu_{H_2O}^R = \mu_{H_2O}^0(T, p_R) - \frac{N_s}{N_{H_2O}} k_B T \approx \mu_{H_2O}^0(T, p_L) + \left( \frac{\partial \mu_{H_2O}^0}{\partial p} \right) (p_R - p_L) - \frac{N_s}{N_{H_2O}} k_B T
  \end{cases}
  \]

  \[
  \Delta p = (p_R - p_L) = \frac{N_s}{V} k_B T
  \]
**Estimate:** Osmotic pressure in an *E. coli* cell

Characteristic concentration of inorganic ions in cells is 100 mM

\[
\frac{N_s}{V} = \frac{100 \times 10^{-3} \times (6 \times 10^{23})}{10^{-3} \text{ m}^3} = 6 \times 10^{25} \text{ m}^{-3} \quad \Rightarrow 6 \times 10^7 \text{ ions/}E. \text{ coli}
\]

\[
\Delta p_{\text{ion}} = (p_{\text{in}} - p_{\text{out}}) = \frac{N_s}{V} k_B T = (6 \times 10^{25}) \times (4 \times 10^{-21}) \text{ Pa}
\]

\[
= 2.4 \times 10^5 \text{ Pa} = 2.4 \text{ atm}
\]

Contributions of other molecules are much smaller than ions

Example: proteins \[
\frac{N_s}{V} = 2 \times 10^6 \text{ ions/}E. \text{ coli}
\]

\[
\Rightarrow \Delta p_{\text{protein}} = 0.08 \text{ atm}
\]

**Remark:** the crowding in cell might change the above results
Entropic force

System $a$: gas+piston

$$S_a = N k_B \ln L + \text{const.}$$

$$U_a = f_{\text{ext}} L + \frac{3}{2} N k_B T$$

$$F_a = f_{\text{ext}} L - T S_a + \frac{3}{2} N k_B T$$

$$\min F_a \Rightarrow f_{\text{ext}} = T \frac{dS_a}{dL} \equiv f_a$$

Formally (形式上), $f_a$ is the force resisting the change of entropy

Called entropic force

What's meaning of $f_a$?

Effective force on the piston by the collisions of gas molecules

Remark: osmotic pressure can also be interpreted as entropic force
If $f_a > f_{ext}$, gas pushes the piston to move and do work against the load

**Question:** Where does the work come from?

- $T$ is fixed $\Rightarrow$ internal energy of the gas molecules is unchanged

\[ \Delta U_{\text{gas}} = W_k + Q = 0 \Rightarrow Q = -W_k > 0 \quad \text{because} \quad W_k < 0 \]

The gas system absorbs thermal energy from the reservoir and converts it into mechanical work

**Question:** Doesn’t that violate the Second Law?

The gas system sacrifices (牺牲) some order in the expansion

**Key point:**

The cost of upgrading energy from thermal to mechanical form is that we must give up order
§6.3 Simple models of ligand-receptor binding & gene expression
### Ligand-receptor binding

#### Lattice model

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<thead>
<tr>
<th>STATE</th>
<th>ENERGY</th>
<th>MULTIPLICITY</th>
<th>WEIGHT</th>
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</thead>
<tbody>
<tr>
<td>(A)</td>
<td>$L\varepsilon_{\text{sol}}$</td>
<td>$\frac{\Omega!}{L!(\Omega-L)!} \approx \frac{\Omega^L}{L!}$</td>
<td>$\frac{\Omega^L}{L!} e^{-\beta L\varepsilon_{\text{sol}}}$</td>
</tr>
<tr>
<td>(B)</td>
<td>$(L-1)\varepsilon_{\text{sol}} + \varepsilon_b$</td>
<td>$\frac{\Omega!}{(L-1)!(\Omega-L+1)!} \approx \frac{\Omega^{L-1}}{(L-1)!}$</td>
<td>$\frac{\Omega^{L-1}}{(L-1)!} e^{-\beta[(L-1)\varepsilon_{\text{sol}} + \varepsilon_b]}$</td>
</tr>
</tbody>
</table>

For $L \ll \Omega$

$$\frac{\Omega!}{(\Omega - L)!} \approx \Omega^L \frac{L!}{(\Omega-L)!}$$

#### Binding probability

$$p_{\text{bound}} = \frac{\Omega^{L-1}}{(L-1)!} \frac{e^{-\beta[(L-1)\varepsilon_{\text{sol}} + \varepsilon_b]}}{(L-1)!} + \frac{\Omega^L}{L!} e^{-\beta L\varepsilon_{\text{sol}}$$
- **Binding curve**

\[ p_{\text{bound}} = \frac{(L/\Omega)e^{-\beta \Delta \varepsilon}}{1 + (L/\Omega)e^{-\beta \Delta \varepsilon}} \]

\[ \Delta \varepsilon = \varepsilon_b - \varepsilon_{\text{sol}} \]

\[ c \equiv \frac{L}{V_{\text{tot}}} \]

\[ c_0 \equiv \frac{\Omega}{V_{\text{tot}}} \]

\[ p_{\text{bound}} = \frac{(c/c_0)e^{-\beta \Delta \varepsilon}}{1 + (c/c_0)e^{-\beta \Delta \varepsilon}} \]

Hill function with Hill coefficient \( n=1 \)

Assume lattice constant \( \sim 1\text{nm} \)

\[ c_0 = \frac{1}{(1\text{ nm})^3} \approx 0.6\text{ M} \]

**Question**: which effect (energy or entropy) dominates at small \( c \)?

**Answer**: entropy
Gene expression

- Genetic control in the central dogma

Very complicated controls, simplified as a problem as RNA polymerase binds at the promoter of the related gene
• Lattice model

Experiment reveals most cellular RNA polymerase molecules are bound to DNA

Assumption: (1) all RNA polymerase molecules are bound to DNA
(2) different binding energies for specific site (promoter) and non-specific sites
(3) \( P \) RNA polymerases and \( N_{NS} \) non-specific sites
- Binding probability of RNA polymerase to its promoter

\[
\rho_{\text{bound}} = \frac{\sum_{\text{states}} \left( \frac{N_{NS}^{P-1}}{P!} \cdot \frac{e^{-(P-1)\varepsilon_{pd}^S/\kappa T} \cdot e^{-\varepsilon_{pd}^S/\kappa T}}{e^{-(P-1)\varepsilon_{pd}^S/\kappa T} \cdot e^{-\varepsilon_{pd}^S/\kappa T}} \right)}{\sum_{\text{states}} \left( \frac{N_{NS}^P}{P!} \cdot \frac{e^{-\varepsilon_{pd}^S/\kappa T}}{e^{-\varepsilon_{pd}^S/\kappa T}} \right) + \sum_{\text{states}} \left( \frac{N_{NS}^{P-1}}{(P-1)!} \cdot \frac{e^{-(P-1)\varepsilon_{pd}^S/\kappa T} \cdot e^{-\varepsilon_{pd}^S/\kappa T}}{e^{-(P-1)\varepsilon_{pd}^S/\kappa T} \cdot e^{-\varepsilon_{pd}^S/\kappa T}} \right)}
\]

Note: The diagram shows the binding process, with states of RNAP and promoter configurations. The equation above is used to calculate the probability of RNAP binding to its promoter. The shapes of the binding curve are determined by the term \( \Delta \varepsilon_{pd} = \varepsilon_{pd}^S - \varepsilon_{pd}^{NS} \).
§6.4 Law of mass action
### Chemical reaction

- **Simple reaction**: $A + B \rightleftharpoons AB$

  Equilibrium at fixed $T$ and $p$

  \[
  \leftrightarrow dG = \left( \frac{\partial G}{\partial N_A} \right)_{T,p} dN_A + \left( \frac{\partial G}{\partial N_B} \right)_{T,p} dN_B + \left( \frac{\partial G}{\partial N_{AB}} \right)_{T,p} dN_{AB} = 0
  \]

  When the numbers of A and B molecules decrease by 1 there is a corresponding increase by 1 in the number of AB molecules.

  Introduce **stoichiometric coefficients** $\nu_A = \nu_B = -1$ and $\nu_{AB} = 1$

  \[
  dN_A = \nu_A dN_{\text{ref}} \quad dN_B = \nu_B dN_{\text{ref}} \quad dN_{AB} = \nu_{AB} dN_{\text{ref}}
  \]

  Chemical potential

  \[
  \mu_A = \left( \frac{\partial G}{\partial N_A} \right)_{T,p} \quad \mu_B = \left( \frac{\partial G}{\partial N_B} \right)_{T,p} \quad \mu_{AB} = \left( \frac{\partial G}{\partial N_{AB}} \right)_{T,p}
  \]

  \[
  \nu_A \mu_A + \nu_B \mu_B + \nu_{AB} \mu_{AB} = 0
  \]
• General reaction

\[ \nu_i X_i \rightleftharpoons 0 \Rightarrow \sum_i \nu_i \mu_i = 0 \]

\[ \mu_i = \mu_i^0 + k_B T \ln \left( \frac{c_i}{c_{i0}} \right) \]

\[ \sum_{i=1}^{N} \nu_i \mu_{i0} = -k_B T \sum_{i=1}^{N} \ln \left( \frac{c_i}{c_{i0}} \right)^{\nu_i} = -k_B T \ln \left[ \prod_{i=1}^{N} \left( \frac{c_i}{c_{i0}} \right)^{\nu_i} \right] \]

\[ \prod_{i=1}^{N} c_i^{\nu_i} = \prod_{i=1}^{N} c_{i0}^{\nu_i} e^{-\beta \sum_{i=1}^{N} \nu_i \mu_{i0}} \equiv K_{eq} \equiv \frac{1}{K_d} \]

equilibrium constant

Law of mass action

dissociation constant
Ligand–Receptor Binding (again)

- Simple binding

\[ L + R \rightleftharpoons LR \]

Law of mass action $\Rightarrow$

\[ K_d = \frac{[L][R]}{[LR]} \]

\[ [LR] = \frac{[L][R]}{K_d} \]

Probability of receptor occupied by ligand

\[ p_{\text{bound}} = \frac{[LR]}{[R] + [LR]} = \frac{[L]/K_d}{1 + ([L]/K_d)} \]

Compare lattice model

\[ p_{\text{bound}} = \frac{(c/c_0)e^{-\beta\Delta \epsilon}}{1 + (c/c_0)e^{-\beta\Delta \epsilon}} \]

\[ K_d = \frac{1}{v} e^{\beta\Delta \epsilon} \]

$\Delta \epsilon (k_B T)$  $K_d (\mu M)$

-12.5  2.2

-10   27

-7.5  330

$\nu$: volume of single lattice
• Cooperative binding—Hill function

\[ L + L + R \rightleftharpoons L_2R \]

Assume: single occupied states are rare

\[ K_d^2 = \frac{[L]^2[R]}{[L_2R]} \]

\[ p_{bound} = \frac{[L_2R]}{[R] + [L_2R]} = \frac{([L]/K_d)^2}{1 + ([L]/K_d)^2} \]

Hill function with \( n=2 \)
§6.5 Discussions on irreversible process
Entropy is not conserved

• Clausius & Kelvin (2nd law)
  - When we release an constraint on an isolated macroscopic system in equilibrium, it eventually reaches a new equilibrium whose entropy is at least as great as before

• Boltzmann (Statistical meaning of entropy)
  - Entropy reflects the disorder of a macroscopic system in equilibrium, when we have limited and coarse knowledge of microstates of the system
• Free expansion of ideal gas

\[ \Delta S = Nk_B \ln 2 \]

Entropy increased spontaneously when we suddenly released a constraint.

The system forfeits (丧失) some order in the free expansion.

**Question:** Would the above process spontaneously happen in reverse?

**Answer:** To get it back, we have to compress the gas with a piston which do mechanical work on the system, heating it up. To return its original state, we then have to cool it (remove some thermal energy).

The cost of recreating order is that we must degrade some organized energy into thermal form. (Lecture 4)
Origin of irreversibility

Increase of entropy $\iff$ Irreversibility in macroscopic process

However, Molecular collisions happens in reverse!
Microscopic equations of motion is reversible!

Puzzle: Where does the irreversibility come from?

Origin of irreversibility: a highly specialized initial state

The instant after the switch is opened, suddenly a huge number of new allowed states appear, and the previously allowed states are suddenly a part of the total allowed states. There is no work-free way (不做功的方式) to suddenly forbid those new states to appear.
• Why can all molecules not go back to the left side spontaneously?

The chance that all molecules in the left side:

\[ P = \left( \frac{1}{2} \right)^N \approx 10^{-N/4} \approx 10^{-10^{22}} \text{ for } N \approx 10^{23} \]

Time scale that we can observe this happens:

\[ \tau = \frac{1}{10^{-10^{22}}} \tau_0 \approx 10^{10^{22}} \text{ s} \gg \tau_{\text{univ}} \approx 200 \times 10^8 \text{ y} \approx 10^{18} \text{ s} \]

\( \tau_0 \) can be taken as the characteristic time (ps) of molecular collisions.
Efficiency of free energy transduction

Initial pressure: \( p_i = \frac{(w_1 + w_2)}{A} \)

Initial height of piston: \( L_i = \frac{N k_B T}{A p_i} \)

Let \( w_2 \) slide away from the piston, and relax gas

Final pressure: \( p_f = \frac{w_1}{A} \)

Final height of piston: \( L_f = \frac{N k_B T}{A p_f} \)

Mechanical work to lift \( w_1 \): \( |\Delta W_k| = w_1 (L_f - L_i) \)

Free energy change of gas: \( |\Delta F| = N k_B T \ln \left( \frac{L_f}{L_i} \right) \)

\( \left| \frac{\Delta W_k}{\Delta F} \right| = ? \)
\[
\frac{\Delta W_k}{\Delta F} = -\frac{x}{\ln(1-x)}
\]

\[x = \frac{w_2}{w_1 + w_2} = \begin{cases} 
0 & \text{for } w_2 = 0 \\
1 & \text{for } w_2 = \infty
\end{cases}
\]

\[|\Delta W_k / \Delta F| \rightarrow 0 \text{ when } w_2 \rightarrow \infty; \quad |\Delta W_k / \Delta F| \rightarrow 1 \text{ when } w_2 \rightarrow 0
\]

Free energy transduction is **least efficient** when it proceeds by the **uncontrolled release of a big constraint**.

Free energy transduction is **most efficient** when it proceeds by the **controlled release of many small constraints step by step**. **“quasi-static process”**!
Heat engine

- Ideal heat engine---Carnot engine

\[
\Delta E_{cycle} = 0
\]

\[
W_{net} = Q_1 - Q_2
\]

\[
\Delta S_{cycle} = 0
\]

\[
\frac{Q_1}{T_1} - \frac{Q_2}{T_2} = 0
\]

\[
\Rightarrow \eta_C = \frac{W_{net}}{Q_1} = \frac{Q_1 - Q_2}{Q_1} = 1 - \frac{T_2}{T_1}
\]
Non-ideal Carnot-like heat engines

\[ \Delta E_{cycle} = Q_1 - Q_2 - W_{net} = 0 \]

\[ W_{net} = Q_1 - Q_2 \]

Non-ideal => irreversible => spontaneous entropy generation

\[ \Delta S^{ir} > 0 \]

\[ \Delta S_{cycle} = \frac{Q_1}{T_1} - \frac{Q_2}{T_2} + \Delta S^{ir} = 0 \]

\[ \Rightarrow \eta = \frac{W_{net}}{Q_1} = \frac{Q_1 - Q_2}{Q_1} = 1 - \frac{Q_2}{Q_1} < 1 - \frac{T_2}{T_1} \equiv \eta_C \]
Efficiency of an engine at maximum power

\[ \eta_{CA} = 1 - \sqrt{\frac{T_2}{T_1}} = 1 - \sqrt{1 - \eta_C}, \quad \text{with} \quad \eta_C = 1 - \frac{T_1}{T_1} \]

Efficiency of a Carnot Engine at Maximum Power Output

<table>
<thead>
<tr>
<th>Power source</th>
<th>( T_2 ) (°C)</th>
<th>( T_1 ) (°C)</th>
<th>( \eta' ) (Eq. 14)</th>
<th>( \eta ) (observed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>West Thurrock (U.K.)² Coal Fired Steam Plant</td>
<td>~25</td>
<td>565</td>
<td>40%</td>
<td>36%</td>
</tr>
<tr>
<td>CANDU (Canada)⁴ PHW Nuclear Reactor</td>
<td>~25</td>
<td>300</td>
<td>28%</td>
<td>30%</td>
</tr>
<tr>
<td>Larderello (Italy)⁶ Geothermal Steam Plant</td>
<td>80</td>
<td>250</td>
<td>17.5%</td>
<td>16%</td>
</tr>
</tbody>
</table>

The efficiency of a Carnot engine is treated for the case where the power output is limited by the rates of heat transfer to and from the working substance. It is shown that the efficiency, \( \eta \), at maximum power output is given by the expression \( \eta = 1 - (T_2/T_1)^{1/2} \) where \( T_1 \) and \( T_2 \) are the respective temperatures of the heat source and heat sink. It is also shown that the efficiency of existing engines is well described by the above result.
During the finite time, the working substance undergoes:

1: isothermal expansion, temperature $T_{1w} < T_1$ (bath)

\[ Q_1 = \alpha (T_1 - T_{1w}) t_1 \]

2: adiabatic expansion, no heat exchange

3: isothermal compression, temperature $T_{2w} > T_2$ (bath)

\[ Q_2 = \beta (T_{2w} - T_2) t_2 \]

4: adiabatic compression, no heat exchange

Total time assumption: $t_{total} = \gamma (t_1 + t_2) \Rightarrow$ Power output: $P = (Q_1 - Q_2) / \gamma (t_1 + t_2)$

Endoreversible assumption: in the above cycle

\[ \Delta S = 0 \Rightarrow \frac{Q_1}{T_{1w}} = \frac{Q_2}{T_{2w}} \]

\[ P = \frac{\alpha \beta xy (T_1 - T_2 - x - y)}{\gamma [\beta T_1 y + \alpha T_2 x + xy (\alpha - \beta)]} \]

\[
\begin{cases}
\text{max}\{P\}: \frac{\partial P}{\partial T_{1w}} = \frac{\partial P}{\partial T_{2w}} = 0 \Rightarrow \frac{T_{2w}}{T_{1w}} = \sqrt{\frac{T_2}{T_1}} \\
\end{cases}
\]

Efficiency at maximum power:

\[ \eta_{CA} = \frac{Q_1 - Q_2}{Q_1} = 1 - \frac{T_{2w}}{T_{1w}} = 1 - \sqrt{\frac{T_2}{T_1}} \]
§ Summary & further reading
Summary

- **Classic thermodynamics**: 0th, 1st, 2nd, 3rd laws

- **Statistical mechanics** for closed system
  - Entropy and Internal energy \( S = -k_B \sum_j P_j \ln P_j \); \( U = \sum_j P_j E_j \)
  - Temperature \( \frac{1}{T} = \left. \frac{\partial S}{\partial U} \right|_V \)
  - Free energy \( F = U - TS = -k_B T \ln Z \)
  - Boltzmann distribution \( P_j = e^{-\beta E_j} / Z \); \( Z = \sum_j e^{-\beta E_j} \)
    - Principle of Min free energy
    - Free energy transduction is most efficient when it proceeds by the controlled release of many small constraints step by step.
• Law of mass action

\[\prod_{i=1}^{N} c_i^{\gamma_i} = \prod_{i=1}^{N} c_{i0}^{\gamma_i} e^{-\beta \sum_{i=1}^{N} \gamma_i \mu_i^0} \equiv K_{eq} \equiv \frac{1}{K_d}\]

• Applications

  - Ideal gas

    \[\frac{U}{N} = \frac{3 k_B T}{2}\]

  - Dilute solution

    \[\mu_i = \mu_{i0} + k_B T \ln \frac{c_i}{c_{i0}}\]

    \[\Delta p = (p_R - p_L) = \frac{N_s V}{k_B T}\]

  - Ligand-receptor simple binding

    \[p_{bound} = \frac{(c/c_0)e^{-\beta \Delta \varepsilon}}{1 + (c/c_0)e^{-\beta \Delta \varepsilon}} = \frac{[L]/K_d}{1 + ([L]/K_d)}\]

  - Gene express (simple model)

    \[p_{bound} = \frac{1}{1 + \frac{NNS}{P} e^{\beta \Delta \varepsilon_{pd}}}\]

  - Ligand-receptor cooperative binding

    \[p_{bound} = \frac{([L]/K_d)^2}{1 + ([L]/K_d)^2}\]
Further reading

- **Phillips** et al., Physical Biology of the Cell, ch6
- **Nelson**, Biological Physics, ch6
- **Lebowitz** (1993) Boltzmann's entropy and time's arrow, Physcis Today 46, 32