

课题组培训

The Cheng Group @ XMU



Introduction to

Statistical Thermodynamics and Free Energy Calculation

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Statistical Thermodynamics

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Basic Concepts

Microstates and Macrostates



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Microstates: each possible configuration
Macrostates: categorization of microstates

Thermal System

Microstates: microscopic configurations
(position and velocity, or energy of every atoms)

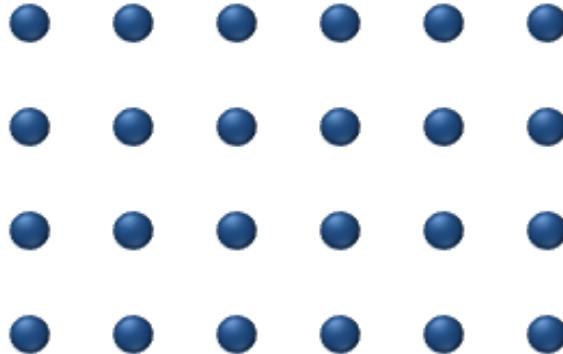
Macrostates: macroscopic properties
(temperature, pressure, total energy, volume...)

Macrostate $E \rightarrow \Omega(E)$ Microstates

Basic Concepts

Thermal fluctuation:

Random deviations of a system from its average state, that occur in a system at equilibrium.



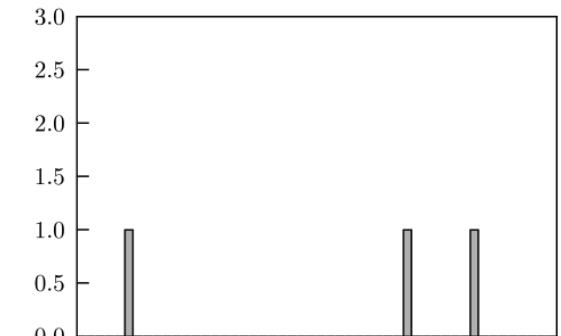
A system at **non-zero** temperature does not stay in its equilibrium microstate, but instead **randomly** samples all possible states.

Thermodynamic limit:

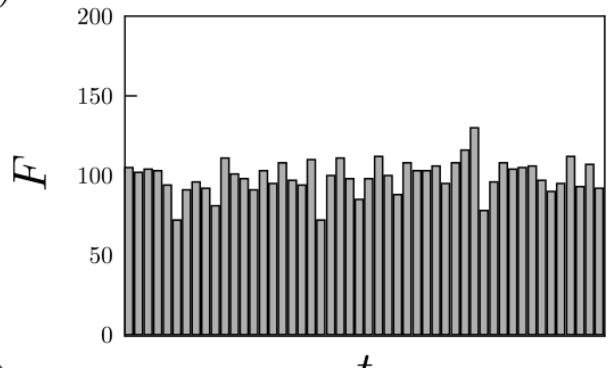
$$\text{pressure} = \frac{\text{Force}}{\text{Area}}$$

$$\text{particle density} = \frac{N}{V}$$

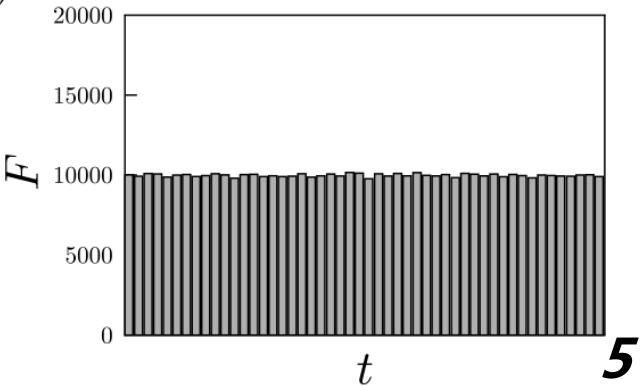
(a)



(b)



(c)



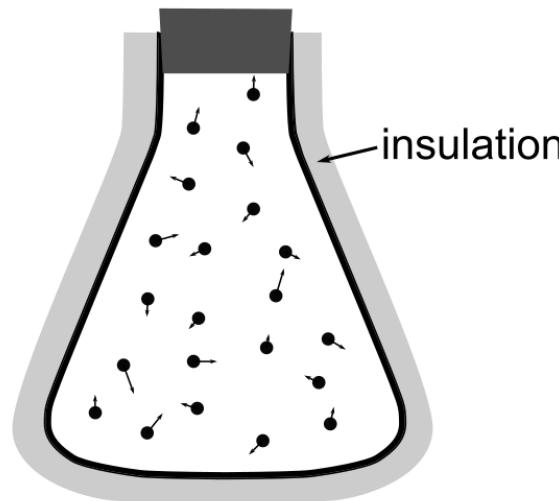
Ensemble

Ensemble is an idealization consisting of *a large number* of virtual copies of a system, each of which represents a *possible* state that the real system *might be in*.

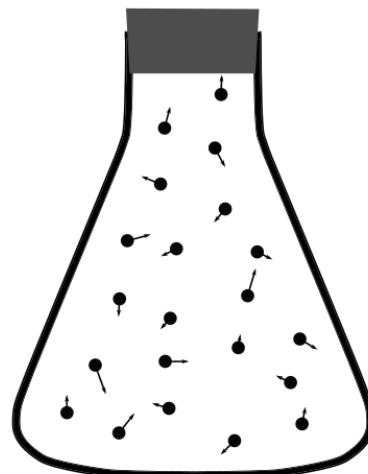
- **The Micro-canonical ensemble (NVE)**: an ensemble of systems that each have the same fixed energy, number of particles and volume.
- **The canonical ensemble(NVT)**: an ensemble of systems that each have fixed temperature, number of particles and volume.
- **The grand canonical ensemble(μ VT)**: an ensemble of systems that each have fixed temperature, volume and chemical potential(μ).

Ensemble

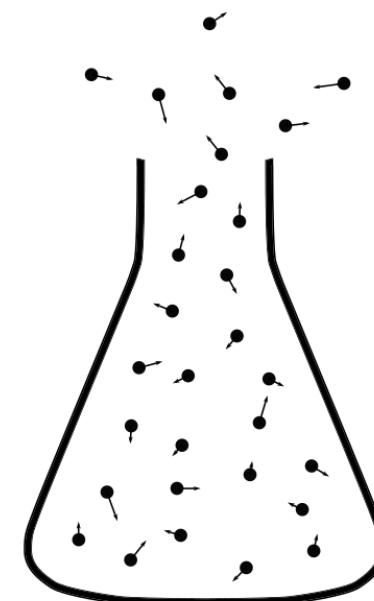
Ensemble is an idealization consisting of *a large number* of virtual copies of a system, each of which represents a *possible* state that the real system *might be in*.



Microcanonical
(const. NVE)



Canonical
(const. NVT)



Grand Canonical
(const. μ VT)

Entropy and Temperature

The number of eigenstates with energy E of a system of N particles in a volume: $\Omega(E, V, N)$.

Entropy: $S \equiv k_B \ln \Omega(E, V, N)$

$$dU = TdS - pdV$$

$$dS = \frac{1}{T}dU - \frac{pdV}{T}$$

Two weakly interacting subsystems

**Micro-canonical Ensemble
NVE**

Total number of degenerate states:

$$\Omega(E, V, N) = \Omega_1(E_1)\Omega_2(E_2)$$

Maximizing: $\frac{d}{dE_1} [\Omega_1(E_1)\Omega_2(E_2)] = 0$

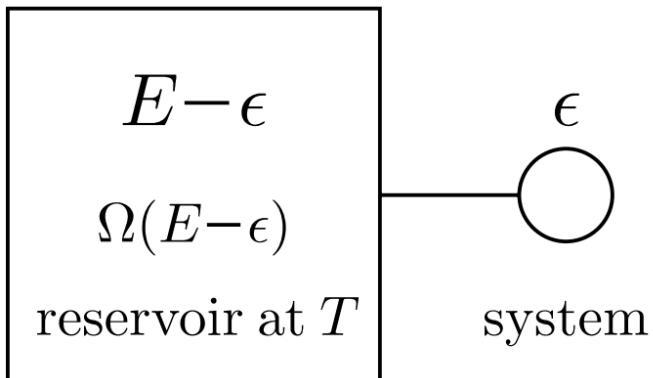
$$\frac{1}{\Omega_1(E_1)} \frac{d \Omega_1(E_1)}{dE_1} + \frac{1}{\Omega_2(E_2)} \frac{d \Omega_2(E_2)}{dE_2} \frac{dE_2}{dE_1} = 0$$

$$E_1 + E_2 = E$$

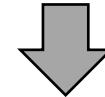
$$\frac{d \ln \Omega_1}{dE_1} = \beta = \frac{d \ln \Omega_2}{dE_2} \quad \beta(E, V, N) = \frac{1}{k_B T} \quad 8$$

Boltzmann Distribution

Canonical ensemble(NVT)



Assumption: for each allowed energy of the system (ϵ) there is only a single microstate, that is $\Omega(\epsilon) = 1$.



$$P(\epsilon) \propto \Omega(E - \epsilon) \times \Omega(\epsilon)$$

Taylor expansion:

$$\boxed{\frac{d\ln\Omega(E)}{dE} = \frac{1}{k_B T}}$$

$$\ln\Omega(E - \epsilon) = \ln\Omega(E) - \frac{d\ln\Omega(E)}{dE} \epsilon + \dots$$

$$\Omega(E - \epsilon) = \Omega(E) e^{-\frac{\epsilon}{k_B T}}$$

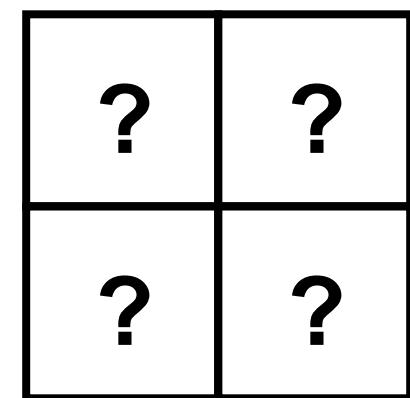
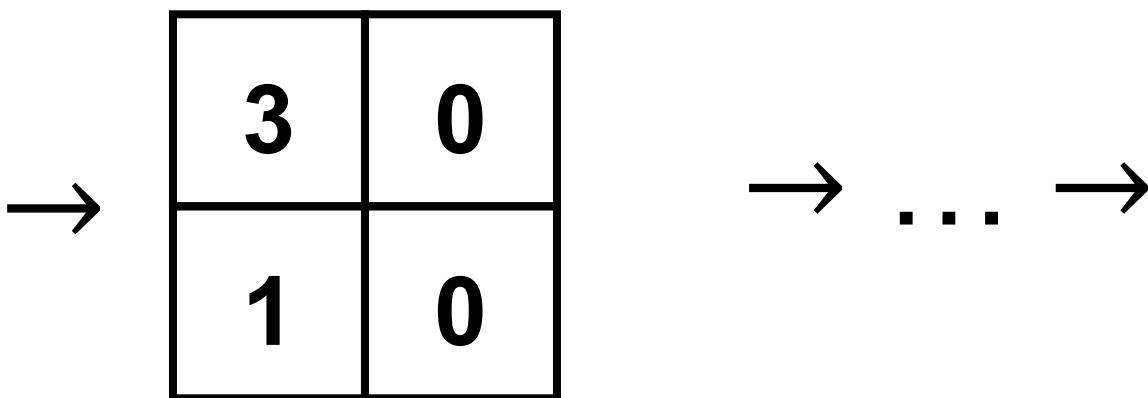
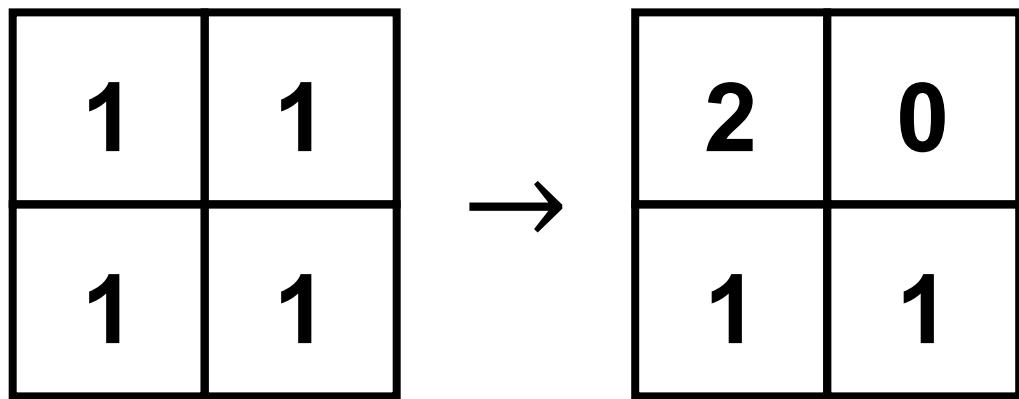
$$P(r) = \frac{\Omega(E - \epsilon_r)}{\sum_i \Omega(E - \epsilon_i)} = \frac{e^{-\frac{\epsilon_r}{k_B T}}}{\sum_i e^{-\frac{\epsilon_i}{k_B T}}}$$

Partition Function: $\sum_i e^{-\frac{\epsilon_i}{k_B T}}$

Boltzmann Distribution

A Boltzmann distribution game

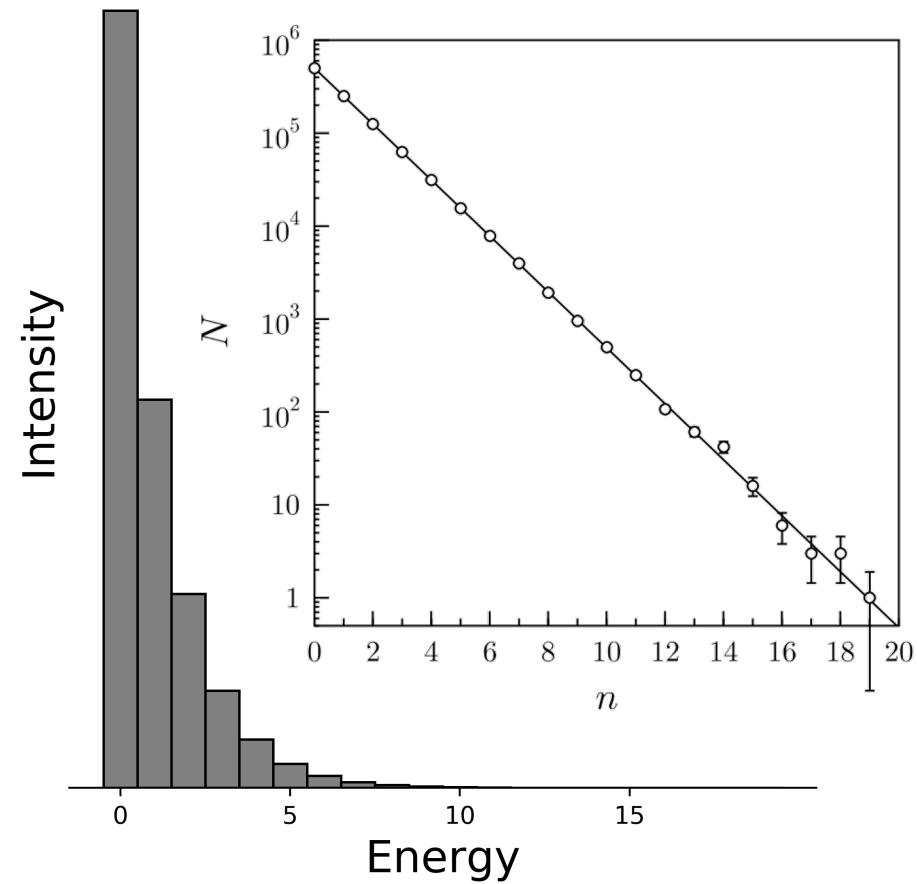
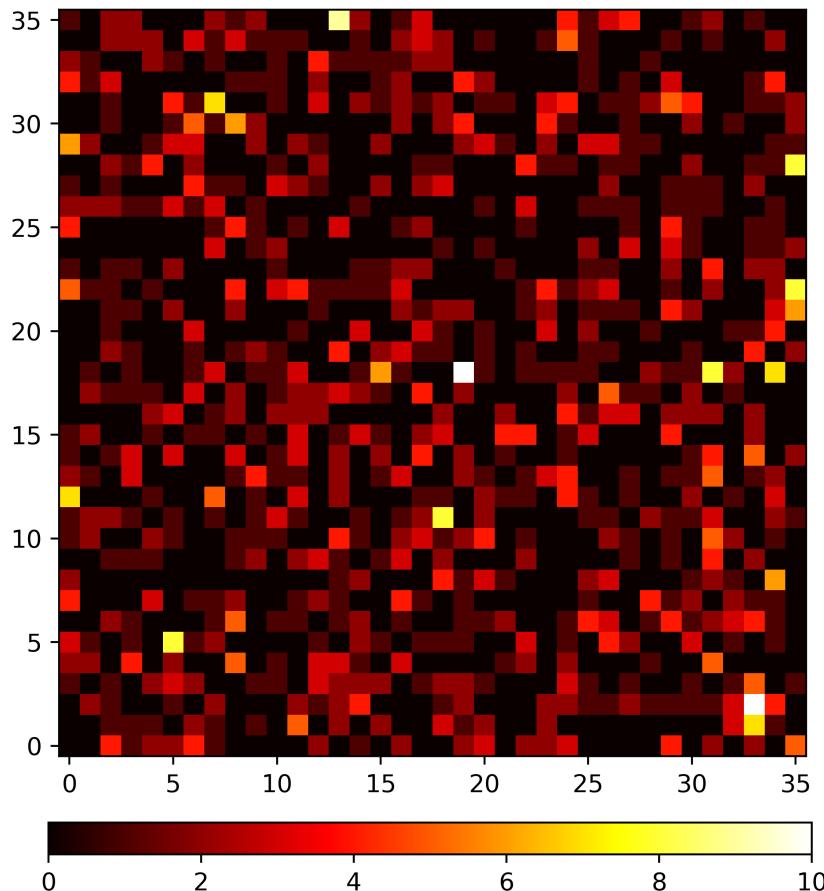
- 1 is “Energy” unit
- “Energy” ≥ 0



Boltzmann Distribution

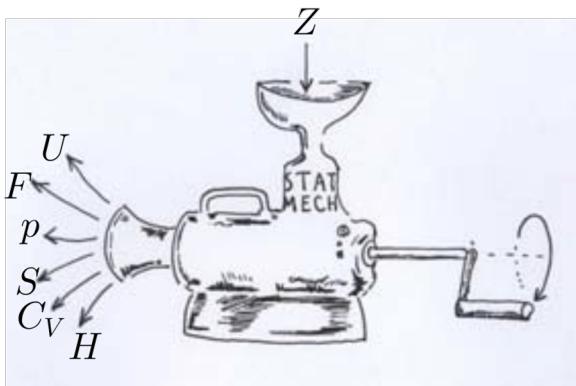
Sampling and plotting with python

36×36 matrix, 1000 times



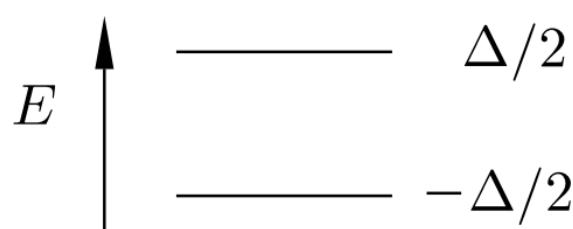
Partition Function

Steps to solving statistical mechanics problems



1. Writing down the **partition function**
2. Obtaining the **functions of state**

(a) The two-level system



$$\begin{aligned} Z &= \sum_{\alpha} e^{-\beta E_{\alpha}} = e^{\frac{\beta \Delta}{2}} + e^{-\frac{\beta \Delta}{2}} \\ &= 2 \cosh\left(\frac{\beta \Delta}{2}\right) \end{aligned}$$

Partition Function → Thermal Functions

Internal energy:

$$U = \sum_i P_i E_i = \frac{\sum_i E_i e^{-\beta E_i}}{\sum_i e^{-\beta E_i}} = - \frac{d \ln Z}{d\beta} = k_B T^2 \frac{d \ln Z}{dT}$$

Entropy:

$$\begin{aligned} S &= \int_0^T \frac{C_V}{T} dT = \int_0^T \frac{1}{T} \left(\frac{\partial U}{\partial T} \right)_V dT = k_B T \frac{d \ln Z}{dT} + k_B \ln Z \\ &= \frac{U}{T} + k_B \ln Z \end{aligned}$$

Helmholtz free energy:

$$A = U - TS = -k_B T \ln Z$$

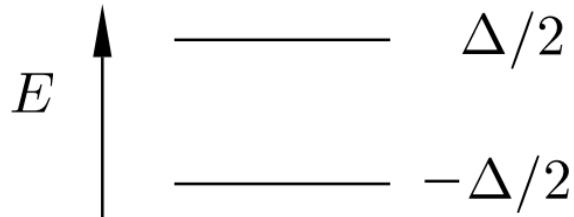
This equation is the workhorse of equilibrium statistical calculation.

Average of thermal function Q :

$$\langle Q \rangle = \sum_i P_i Q_i = \frac{\sum_i Q_i e^{-\beta E_i}}{\sum_i e^{-\beta E_i}}$$

Partition Function → Thermal Functions

The two-level system

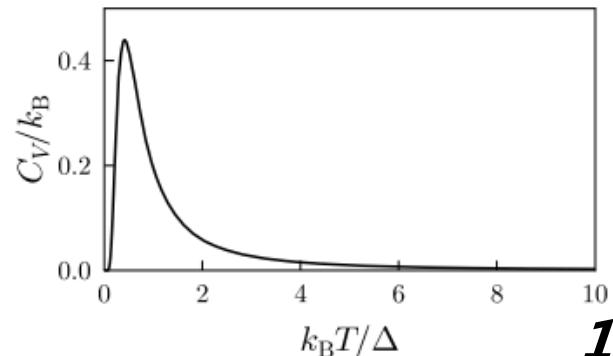
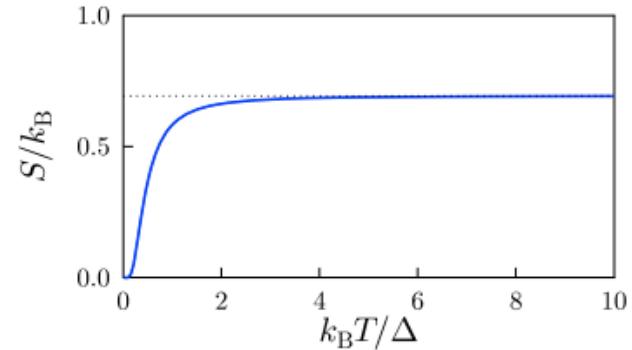
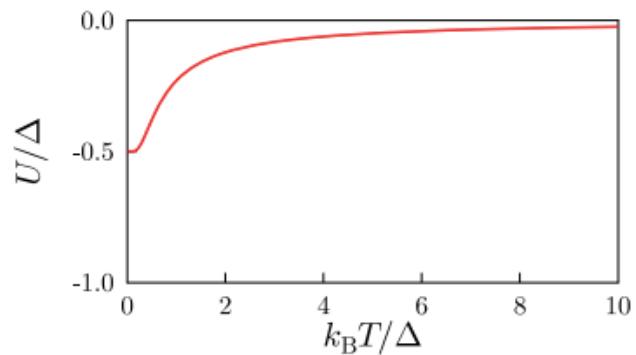


$$Z = 2 \cosh\left(\frac{\beta\Delta}{2}\right)$$

$$U = -\frac{d \ln Z}{d\beta} = -\frac{\Delta}{2} \tanh\left(\frac{\beta\Delta}{2}\right)$$

$$S = -\frac{\Delta}{2T} \tanh\left(\frac{\beta\Delta}{2}\right) + k_B T \ln\left[2 \cosh\left(\frac{\beta\Delta}{2}\right)\right]$$

$$C_V = \left(\frac{\partial U}{\partial T}\right)_V = k_B \left(\frac{\beta\Delta}{2}\right)^2 \operatorname{sech}\left(\frac{\beta\Delta}{2}\right)$$



Grand Partition Function

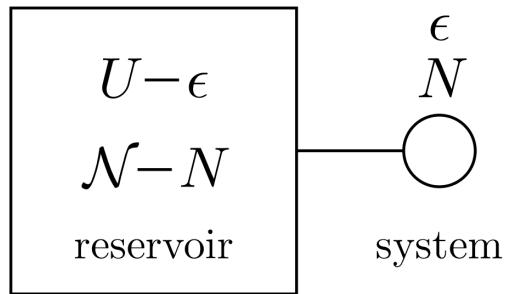
$$dU = TdS - pdV + \mu dN$$

$$S = k_B \ln \Omega(U, V, N)$$

$$dS = \left(\frac{\partial S}{\partial U}\right)_{N,V} dU + \left(\frac{\partial S}{\partial V}\right)_{N,U} dV + \left(\frac{\partial S}{\partial N}\right)_{U,V} dN$$

$$= \frac{dU}{T} + \frac{pdV}{T} - \frac{\mu dN}{T}$$

Grand Canonical Ensemble:



$$\begin{aligned} S(U - \epsilon, \mathcal{N} - N) &= S(U, \mathcal{N}) - \epsilon \left(\frac{\partial S}{\partial U}\right)_{\mathcal{N}, V} - n \left(\frac{\partial S}{\partial \mathcal{N}}\right)_{U, V} \\ &= S(U, \mathcal{N}) - \frac{1}{T}(\epsilon - \mu N) \end{aligned}$$

$$P(\epsilon, n) \propto e^{S(U - \epsilon, \mathcal{N} - N)/k_B} \propto e^{\beta(\mu N - \epsilon)}$$

Grand Partition Function: $\mathcal{Z} = \sum_i e^{\beta(\mu N_i - E_i)}$

Grand Potential: $\Phi_G = -k_B T \ln \mathcal{Z}$

Fermions and Bosons

Fermions: $\hat{P}_{12} |\psi\rangle = -|\psi\rangle$

Bosons: $\hat{P}_{12} |\psi\rangle = |\psi\rangle$

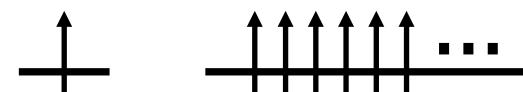
If $\psi = |\phi\rangle|\phi\rangle$, then

$$\hat{P}_{12} |\phi\rangle|\phi\rangle = -|\phi\rangle|\phi\rangle = |\phi\rangle|\phi\rangle$$

$$|\phi\rangle|\phi\rangle = 0$$

For fermions, the doubly-occupied state cannot exist. e.g. electron.

For bosons, there is not such constraint. e.g. photon.



Statistics of identical particles

Assumption: there is only one energy level. $\rightarrow \mathcal{Z} = \sum_n e^{n\beta(\mu-E)}$

$$\langle n \rangle = \frac{\sum_n n e^{n\beta(\mu-E)}}{\sum_n e^{n\beta(\mu-E)}}$$

$$= -\frac{1}{\beta} \frac{\partial \ln \mathcal{Z}}{\partial E}$$

Fermions: $n = 0$ or 1

$$\mathcal{Z}_{fermions} = 1 + e^{\beta(\mu-E)}$$

Bosons: $n = 0, 1, 2, 3 \dots$

$$\mathcal{Z}_{bosons} = \frac{1}{1 - e^{\beta(\mu-E)}}$$

Fermions and Bosons

Fermions:

$$\langle n \rangle = -\frac{1}{\beta} \frac{\partial \ln \mathcal{Z}}{\partial E}$$

$$\ln \mathcal{Z}_{fermions} = \ln[1 + e^{\beta(\mu-E)}]$$

$$\langle n \rangle_{fermion} = \frac{e^{\beta(\mu-E)}}{1 + e^{\beta(\mu-E)}} = \frac{1}{e^{\beta(E-\mu)} + 1}$$

Bosons:

$$\ln \mathcal{Z}_{bosons} = -\ln[1 - e^{\beta(\mu-E)}]$$

$$\langle n \rangle_{bosons} = \frac{e^{\beta(\mu-E)}}{1 - e^{\beta(\mu-E)}} = \frac{1}{e^{\beta(E-\mu)} - 1}$$

For one quantum state:

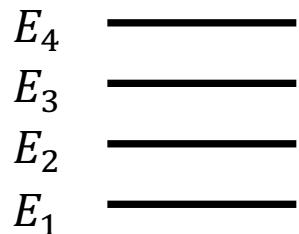
$$\langle n \rangle = \frac{1}{e^{\beta(E-\mu)} \pm 1} \quad \begin{aligned} &+ \text{ for fermions} \\ &- \text{ for bosons} \end{aligned}$$

Fermions and Bosons

For many quantum states:

⋮

a particular configuration of the system:



$$[e^{\beta(\mu-E_1)}]^{n_1} \times [e^{\beta(\mu-E_2)}]^{n_2} \times \dots = \prod_i e^{n_i \beta(\mu-E_i)}$$

occupation number n_i



Partition function: $\mathcal{Z} = \sum_{\{n_i\}} \prod_i e^{n_i \beta(\mu-E_i)} = \prod_i \sum_{\{n_i\}} e^{n_i \beta(\mu-E_i)}$

$\sum_i n_i$ does not have to be fixed.

For Fermions: $\{n_i\} = \{0, 1\}$

For Bosons: $\{n_i\} = \{0, 1, 2, 3, \dots\}$

Fermions and Bosons

For Fermions: $\{n_i\} = \{0, 1\}$

$$\mathcal{Z}_{fermions} = \prod_i [1 + e^{\beta(\mu - E_i)}] \quad \ln \mathcal{Z}_{fermions} = \sum_i \ln[1 + e^{\beta(\mu - E_i)}]$$

$$\langle n_i \rangle_{fermions} = -\frac{1}{\beta} \frac{\partial \ln \mathcal{Z}}{\partial E_i} = \frac{e^{\beta(\mu - E_i)}}{1 + e^{\beta(\mu - E_i)}} = \frac{1}{e^{\beta(E_i - \mu)} + 1}$$

For Bosons: $\{n_i\} = \{0, 1, 2, 3, \dots\}$

$$\mathcal{Z}_{bosons} = \prod_i [1 + e^{\beta(\mu - E_i)} + e^{2\beta(\mu - E_i)} + \dots] = \prod_i \frac{1}{1 - e^{\beta(\mu - E_i)}}$$

$$\ln \mathcal{Z}_{bosons} = -\sum_i \ln[1 - e^{\beta(\mu - E_i)}]$$

$$\langle n_i \rangle_{bosons} = -\frac{1}{\beta} \frac{\partial \ln \mathcal{Z}}{\partial E_i} = \frac{e^{\beta(\mu - E_i)}}{1 - e^{\beta(\mu - E_i)}} = \frac{1}{e^{\beta(E_i - \mu)} - 1}$$

Fermions and Bosons

Distribution Function: $f(E) = \langle n \rangle$

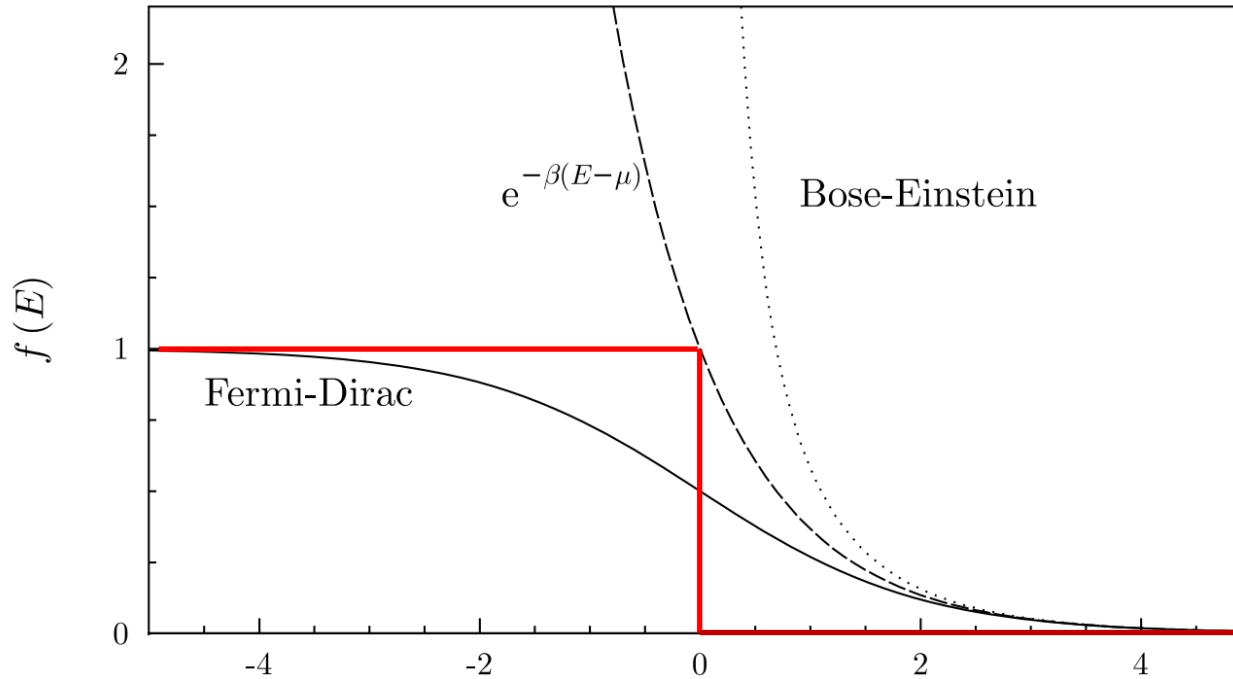
$$\beta = \frac{1}{k_B T}$$

$$f(E) = \frac{1}{e^{\beta(E-\mu)} + 1}$$

Fermi-Dirac Distribution function

$$f(E) = \frac{1}{e^{\beta(E-\mu)} - 1}$$

Bose-Einstein Distribution function



Questions

在边长为a的一维势箱中运动的离子为一维平动子，其平动能公式为
 $(\epsilon_t)_x = \frac{h^2 n_x^2}{8ma^2}$ ，式中h为普朗克常数，m为粒子质量， n_x 为量子数($n_x = 1, 2, 3, \dots, \infty$)，求一维平动子的平动配分函数。

解：

$$(q_t)_x = \sum_{n_x=1}^{\infty} e^{-\frac{h^2 n_x^2}{8ma^2 k_B T}} = \sum_{n_x=1}^{\infty} e^{-An_x^2}$$

由于平动能的间距很小： $(q_t)_x = \int_0^{\infty} e^{-\frac{h^2 n_x^2}{8ma^2 k_B T}} dn_x = \int_0^{\infty} e^{-An_x^2} dn_x$

$$\int_0^{\infty} e^{-Ax^2} dx = \frac{1}{2} \sqrt{\frac{\pi}{A}} \quad \dashrightarrow \quad (q_t)_x = \left(\frac{2\pi m k_B T}{h^2} \right)^{\frac{1}{2}} a$$

Questions

三维势箱中平动子的能量为: $\epsilon = (\epsilon_t)_x + (\epsilon_t)_y + (\epsilon_t)_z = \frac{h^2}{8m} \left(\frac{n_x^2}{a^2} + \frac{n_y^2}{b^2} + \frac{n_z^2}{c^2} \right)$,
求三维平动子的平动配分函数。

解:

$$q_t = \sum_{n_x=1}^{\infty} \sum_{n_y=1}^{\infty} \sum_{n_z=1}^{\infty} e^{-\frac{h^2}{8mk_B T} \left(\frac{n_x^2}{a^2} + \frac{n_y^2}{b^2} + \frac{n_z^2}{c^2} \right)} = \sum_{n_x=1}^{\infty} e^{-B \frac{n_x^2}{a^2}} \sum_{n_y=1}^{\infty} e^{-B \frac{n_y^2}{b^2}} \sum_{n_z=1}^{\infty} e^{-B \frac{n_z^2}{c^2}}$$

$$q_t = (q_t)_x (q_t)_y (q_t)_z = \left[\left(\frac{2\pi m k_B T}{h^2} \right)^{\frac{1}{2}} a \right] \left[\left(\frac{2\pi m k_B T}{h^2} \right)^{\frac{1}{2}} b \right] \left[\left(\frac{2\pi m k_B T}{h^2} \right)^{\frac{1}{2}} c \right]$$

$$= \left(\frac{2\pi m k_B T}{h^2} \right)^{\frac{3}{2}} abc = \left(\frac{2\pi m k_B T}{h^2} \right)^{\frac{3}{2}} V$$

理想气体配分函数

对于 N 个 可分辨粒子:

$$Q_t = (q_t)^N = \left[\left(\frac{2\pi m k_B T}{h^2} \right)^{\frac{3}{2}} V \right]^N$$

对于 N 个 全同粒子:

$$Q_t = \frac{(q_t)^N}{N!} = \frac{1}{N!} \left[\left(\frac{2\pi m k_B T}{h^2} \right)^{\frac{3}{2}} V \right]^N$$



Summary

Canonical partition function: $Z = \sum_i e^{-\frac{E_i}{k_B T}}$

Helmholtz free energy: $A = U - TS = -k_B T \ln Z$

Grand Partition Function: $\mathcal{Z} = \sum_i e^{\beta(\mu N_i - E_i)}$

Grand Potential: $\Phi_G = -k_B T \ln \mathcal{Z}$

Fermi-Dirac Distribution: $f(E) = \frac{1}{e^{\beta(E-\mu)} + 1}$

Bose-Einstein Distribution: $f(E) = \frac{1}{e^{\beta(E-\mu)} - 1}$

Partition Function → Thermodynamics

Free Energy Calculation

Excess Partition Function

Phase space: “For mechanical systems, the phase space usually consists of all possible values of position and momentum variables”.

$$Q_{NVT} = \frac{1}{N!} \frac{1}{h^{3N}} \iint d\mathbf{p}^N d\mathbf{r}^N \exp\left[-\frac{\mathcal{H}(\mathbf{p}^N, \mathbf{r}^N)}{k_B T}\right]$$

Configuration space: \mathbf{r}^N
Momentum space: \mathbf{p}^N
Phase space: $\mathbf{p}^N, \mathbf{r}^N$

$$\mathcal{H}(\mathbf{p}^N, \mathbf{r}^N) = \sum_{i=1}^N \frac{|\mathbf{p}_i|^2}{2m_i} + \mathcal{V}(\mathbf{r}^N)$$

$\mathcal{V}(\mathbf{r}^N)$ is independent upon the velocities of atoms

$$Q_{NVT} = \frac{1}{N!} \frac{1}{h^{3N}} \int d\mathbf{p}^N \exp\left[-\frac{|\mathbf{p}|^2}{2mk_B T}\right] \int d\mathbf{r}^N \exp\left[-\frac{\mathcal{V}(\mathbf{r}^N)}{k_B T}\right]$$

$$\int d\mathbf{p}^N \exp\left[-\frac{|\mathbf{p}|^2}{2mk_B T}\right] = (2\pi mk_B T)^{3N/2}$$

$$Q_{NVT} = \frac{1}{N!} \left(\frac{2\pi mk_B T}{h^2} \right)^{3N/2} \int d\mathbf{r}^N \exp\left[-\frac{\mathcal{V}(\mathbf{r}^N)}{k_B T}\right]$$

N ideal gas particles:

$$Q_{NVT}^{ideal} = \frac{V^N}{N!} \left(\frac{2\pi mk_B T}{h^2} \right)^{3N/2}$$

$$Q_{NVT} = Q_{NVT}^{ideal} Q_{NVT}^{excess}$$

$$Q_{NVT}^{excess} = \frac{1}{V^N} \int d\mathbf{r}^N \exp\left[-\frac{\mathcal{V}(\mathbf{r}^N)}{k_B T}\right]$$

Free Energy Difference

$$A = -k_B T \ln Q_{NVT} \quad \rightarrow \quad \Delta A = A_Y - A_X = -k_B T \ln \frac{Q_Y}{Q_X}$$

$$\begin{aligned}\Delta A &= -k_B T \ln \frac{\iint d\mathbf{p}^N d\mathbf{r}^N \exp[-\frac{\mathcal{H}_Y(\mathbf{p}^N, \mathbf{r}^N)}{k_B T}]}{\iint d\mathbf{p}^N d\mathbf{r}^N \exp[-\frac{\mathcal{H}_X(\mathbf{p}^N, \mathbf{r}^N)}{k_B T}]} \\ &= -k_B T \ln \frac{\iint d\mathbf{p}^N d\mathbf{r}^N \exp[-\frac{\mathcal{H}_Y(\mathbf{p}^N, \mathbf{r}^N)}{k_B T}] \exp[+\frac{\mathcal{H}_X(\mathbf{p}^N, \mathbf{r}^N)}{k_B T}] \exp[-\frac{\mathcal{H}_X(\mathbf{p}^N, \mathbf{r}^N)}{k_B T}]}{\iint d\mathbf{p}^N d\mathbf{r}^N \exp[-\frac{\mathcal{H}_X(\mathbf{p}^N, \mathbf{r}^N)}{k_B T}]} \\ &= -k_B T \ln \frac{\iint d\mathbf{p}^N d\mathbf{r}^N \exp[-\frac{\mathcal{H}_Y(\mathbf{p}^N, \mathbf{r}^N) - \mathcal{H}_X(\mathbf{p}^N, \mathbf{r}^N)}{k_B T}] \exp[-\frac{\mathcal{H}_X(\mathbf{p}^N, \mathbf{r}^N)}{k_B T}]}{\iint d\mathbf{p}^N d\mathbf{r}^N \exp[-\frac{\mathcal{H}_X(\mathbf{p}^N, \mathbf{r}^N)}{k_B T}]}\end{aligned}$$

$$\boxed{\langle Q \rangle = \sum_i P_i Q_i = \frac{\sum_i Q_i e^{-\beta E_i}}{\sum_i e^{-\beta E_i}}}$$

Averaging over the ensemble configuration representative of **initial state X**.

Free Energy Difference

$$\Delta A = -k_B T \ln \langle \exp[-(\mathcal{H}_Y - \mathcal{H}_X)/k_B T] \rangle_X$$

$$\Delta A = k_B T \ln \langle \exp[-(\mathcal{H}_X - \mathcal{H}_Y)/k_B T] \rangle_Y$$

$\langle \rangle_X$ means the **average** over the potential energy surface X.

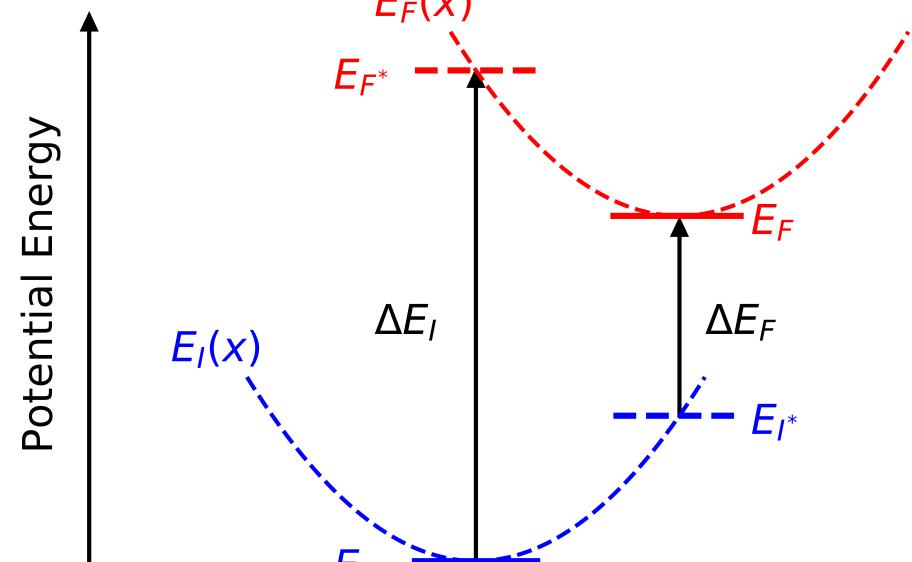
Such an average over *all possible quantum states* of a system is called an **ensemble average**.

$$\Delta A = A_Y - A_X = -k_B T \ln \frac{Q_Y}{Q_X}$$

↓
 $Q_{NVT} = Q_{NVT}^{ideal} Q_{NVT}^{excess}$
↓

$$\Delta A = -k_B T \ln \left\langle \exp \left[-\frac{\Delta E}{k_B T} \right] \right\rangle_X$$

ΔE is Potential Energy Difference



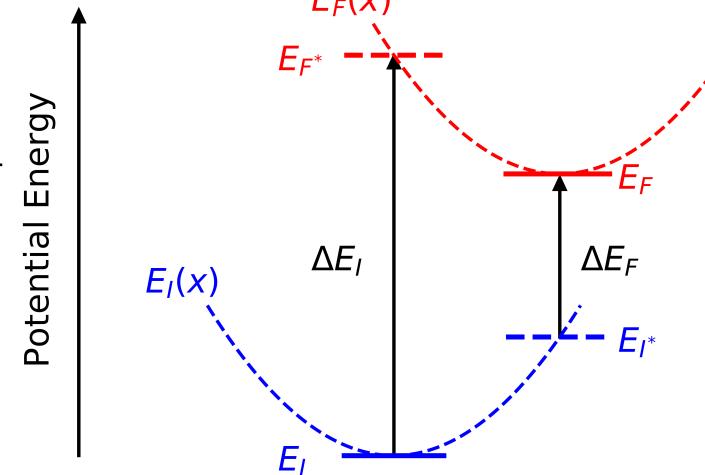
Free Energy Difference

$$\Delta A = A_Y - A_X = -k_B T \ln \frac{Q_Y}{Q_X} = -k_B T \ln \frac{Q_{Y, NVT}^{excess}}{Q_{X, NVT}^{excess}}$$

$$= -k_B T \ln \frac{\int d\mathbf{r}^N \exp[-\frac{\mathcal{V}_Y(\mathbf{r}^N) - \mathcal{V}_X(\mathbf{r}^N)}{k_B T}] \exp[-\frac{\mathcal{V}_X(\mathbf{r}^N)}{k_B T}]}{\int d\mathbf{r}^N \exp[-\frac{\mathcal{V}_X(\mathbf{r}^N)}{k_B T}]}$$

$$= -k_B T \ln \frac{\int d\mathbf{r}^N \exp[-\frac{\Delta E}{k_B T}] \exp[-\frac{\mathcal{V}_X(\mathbf{r}^N)}{k_B T}]}{\int d\mathbf{r}^N \exp[-\frac{\mathcal{V}_X(\mathbf{r}^N)}{k_B T}]}$$

$$= -k_B T \ln \left\langle \exp \left[-\frac{\Delta E}{k_B T} \right] \right\rangle_X$$

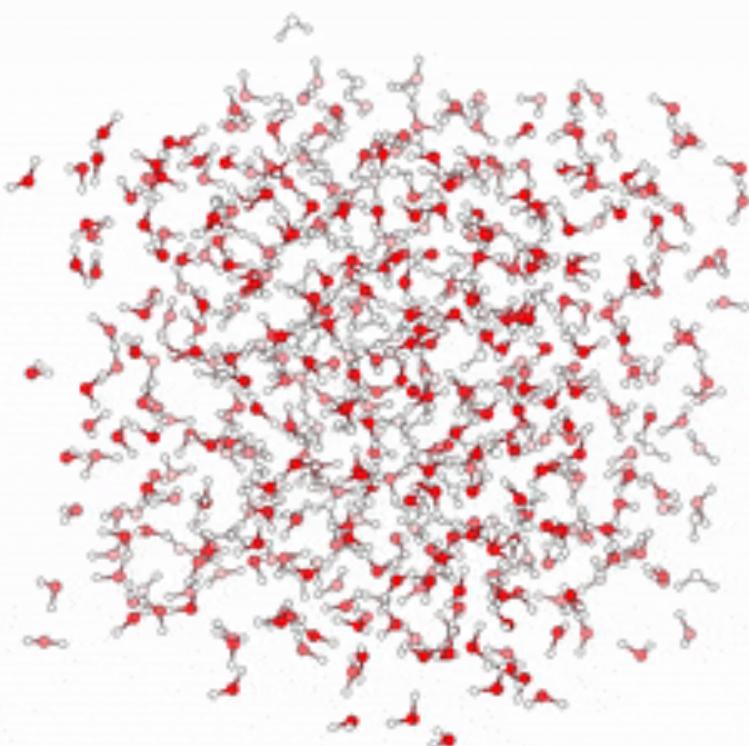


Molecular Dynamics and Monte Carlo Sampling

“This simplification is true for any two systems of particles with the same masses.”

Molecular Dynamics

$$m_i \ddot{\mathbf{r}}_i = \mathbf{f}_i \quad \mathbf{f}_i = -\frac{\partial}{\partial \mathbf{r}_i} \mathcal{V}$$



Initialize: Initial particle positions, velocities ...

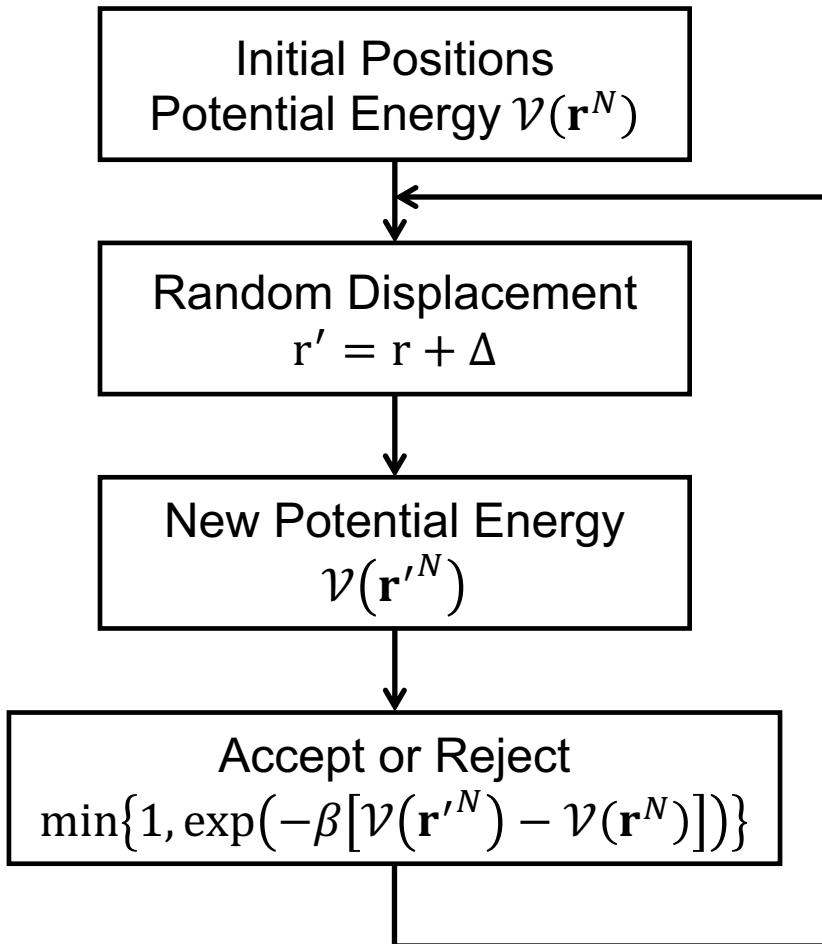
Calculate forces from particle positions

Solve Newton's eqns. of motion (integrate)

Perform analysis / Write data to disk

Loop over time-steps

Monte Carlo Sampling

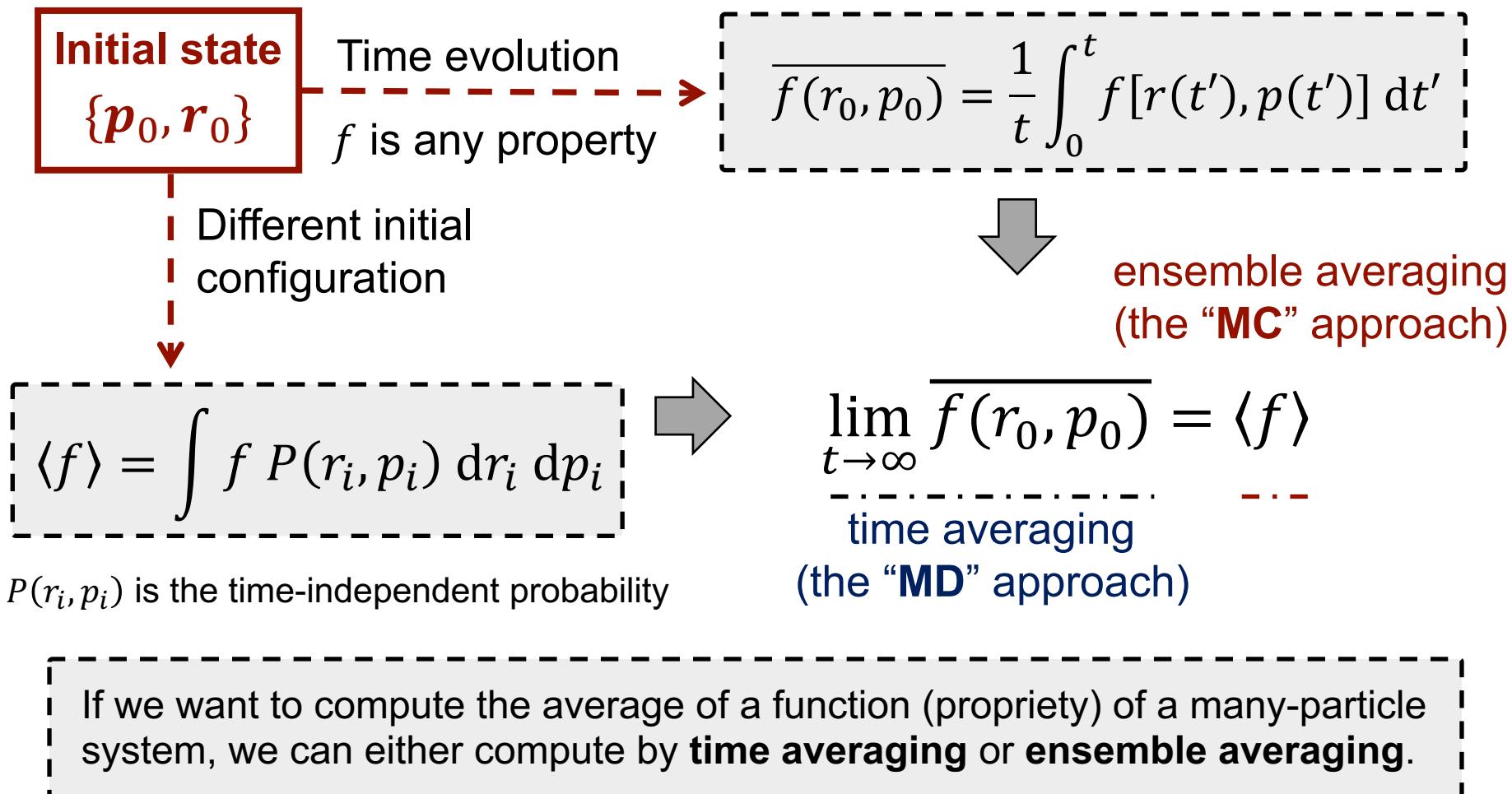


SUBROUTINE mcmove

```
o=int(ranf()*npart)+1
call ener(x(o),eno)
xn=x(o)+(ranf()-0.5)*delx
call ener(xn,enn)
if (ranf().lt.exp(-beta
+ * (enn-eno)) x(o)=xn
return
end
```

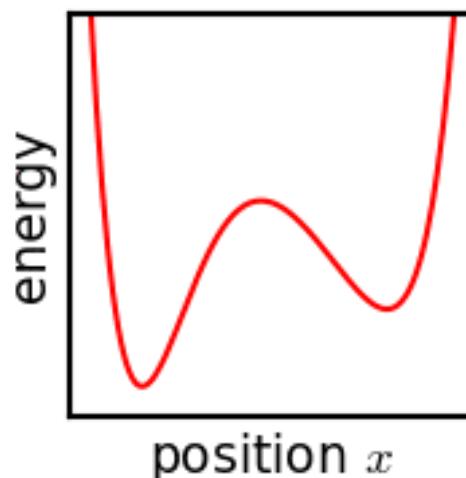
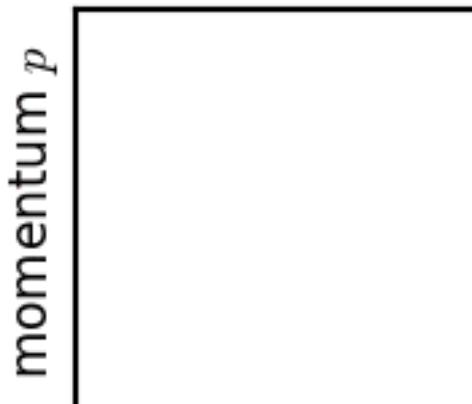
Ergodicity

Ergodic hypothesis: “over long periods of time, all accessible microstates are equiprobable”.

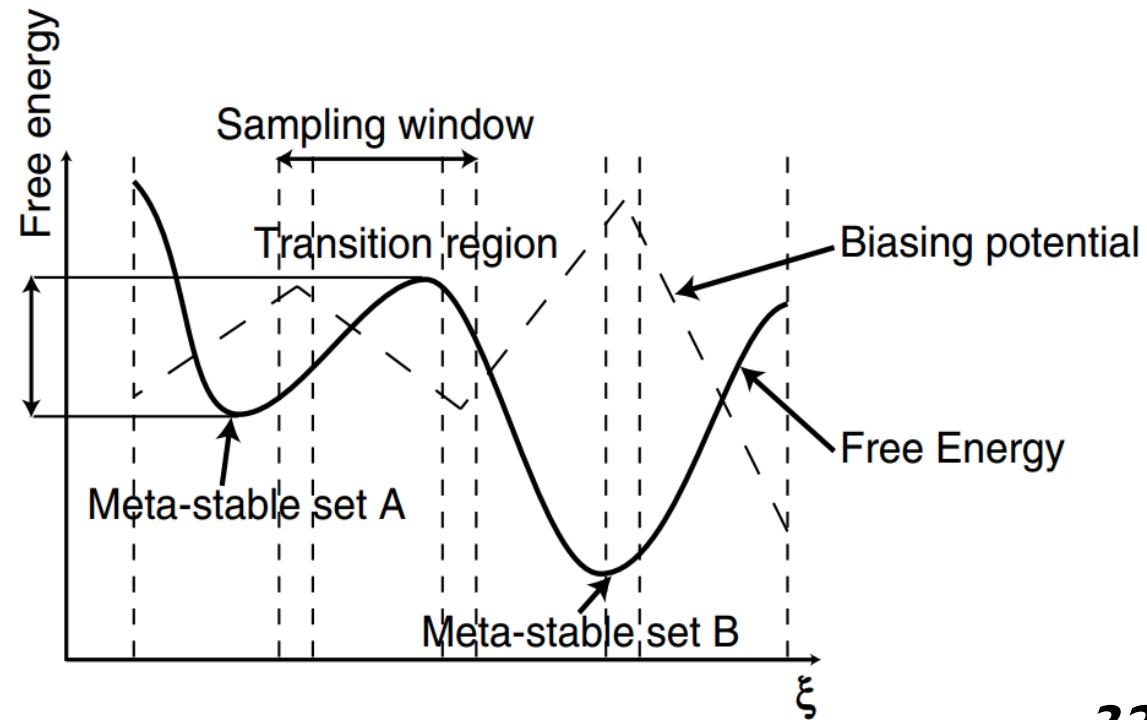


Nonergodicity

Quasi-nonergodicity: *The system does not properly explore phase space.*



*The appearance of **nonergodicity** is usually caused by **high energy barriers** separating different volumes of phase space.*

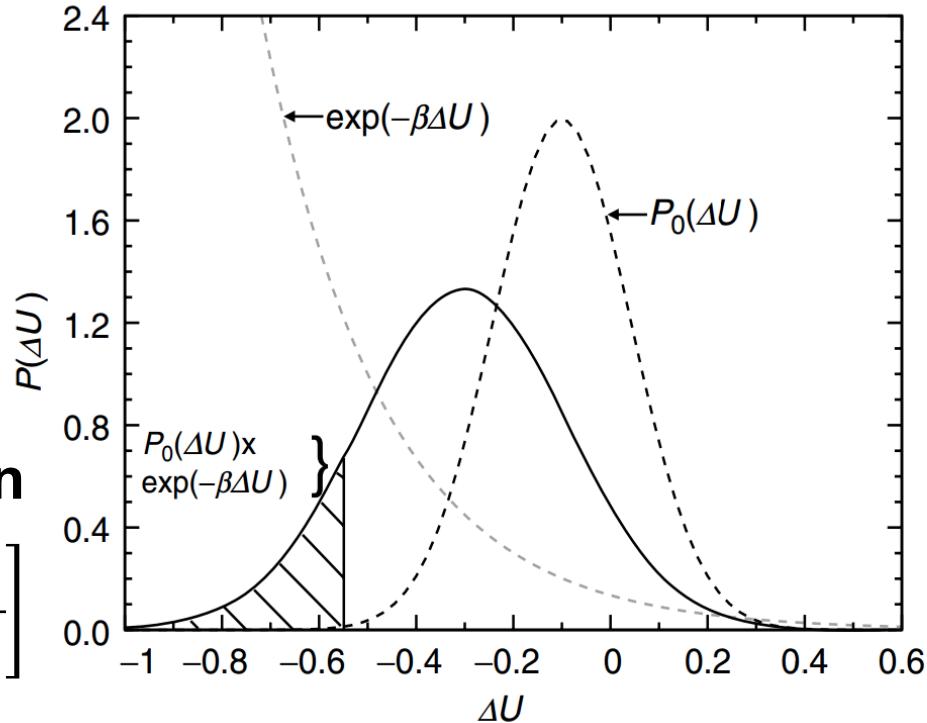


Nonergodicity

$$\Delta A = -k_B T \ln \frac{\int \mathbf{d}\mathbf{r}^N \exp\left[-\frac{\Delta E}{k_B T}\right] \exp\left[-\frac{\mathcal{V}_X}{k_B T}\right]}{\int d\mathbf{r}^N \exp\left[-\frac{\mathcal{V}_X}{k_B T}\right]}$$
$$= -k_B T \ln \int \exp\left[-\frac{\Delta E}{k_B T}\right] P_0(\Delta E) d\Delta E$$

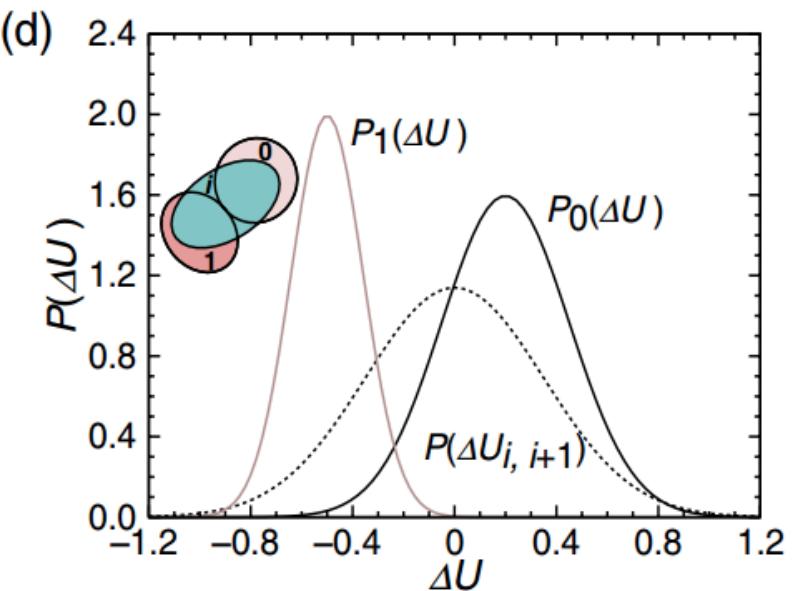
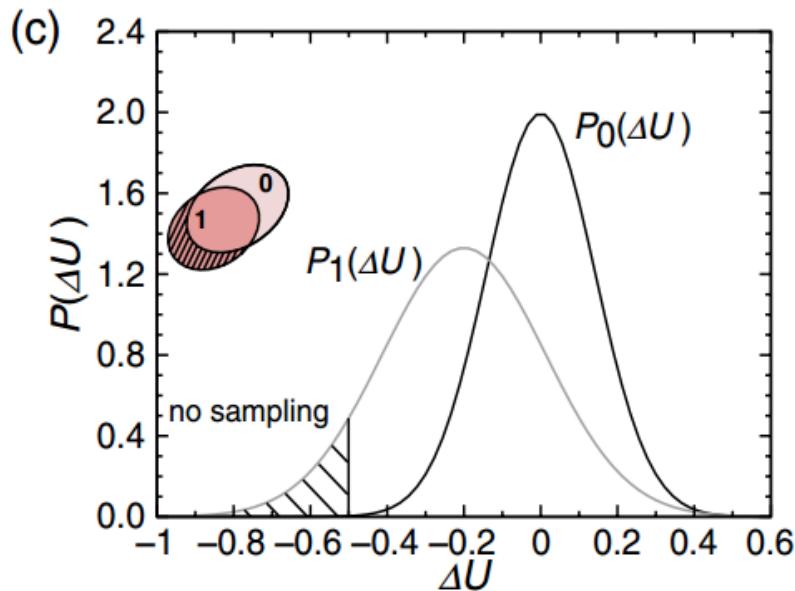
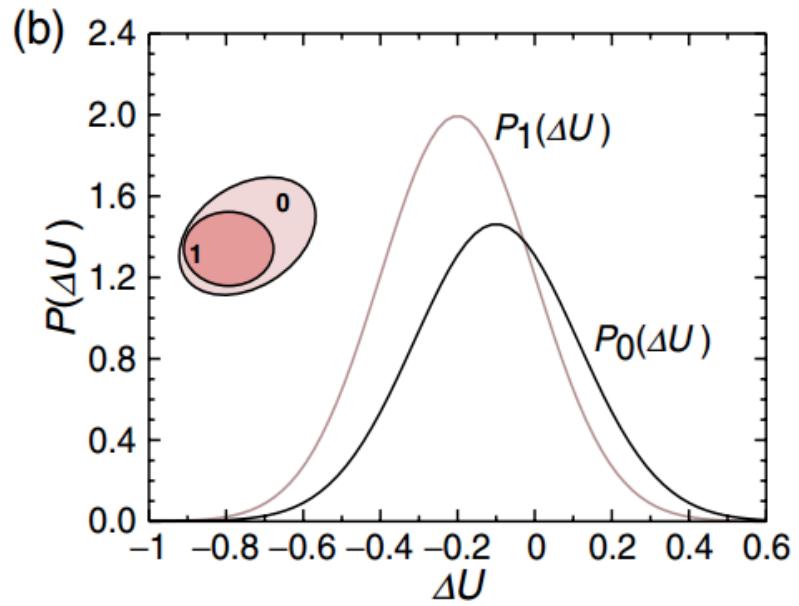
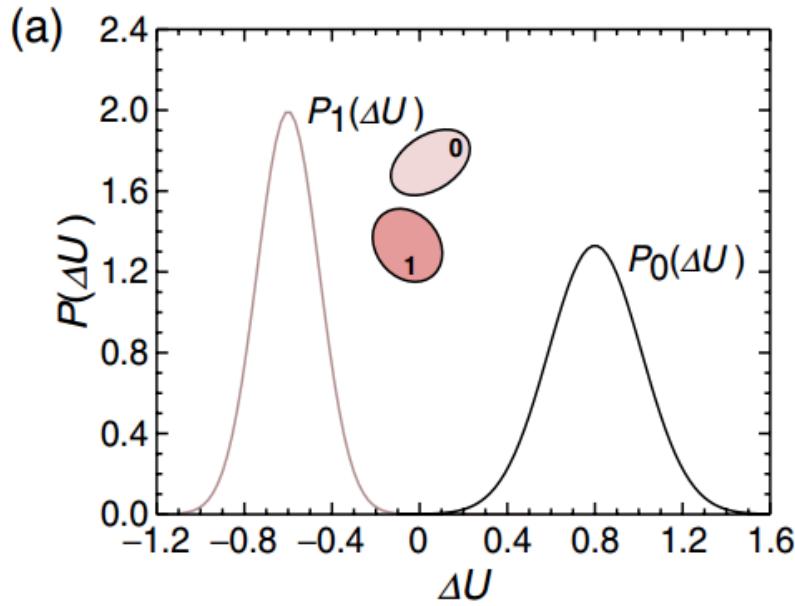
Assumption: $P_0(\Delta E)$ is a **Gaussian**

$$P_0(\Delta E) = \frac{1}{\sqrt{2\pi}\sigma} \exp\left[-\frac{(\Delta E - \langle \Delta E \rangle_0)^2}{2\sigma^2}\right]$$



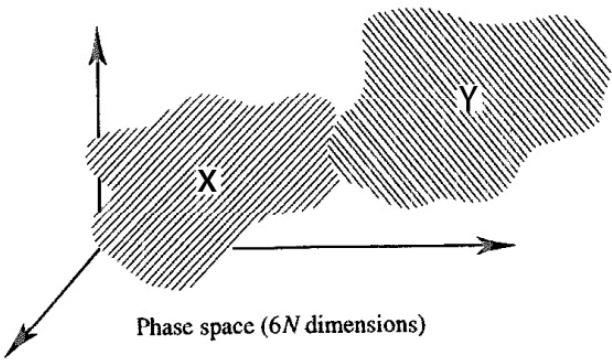
The **low- ΔE** tail of the integrand, marked with stripes is poorly sampled with $P_0(\Delta E)$

Important Regions

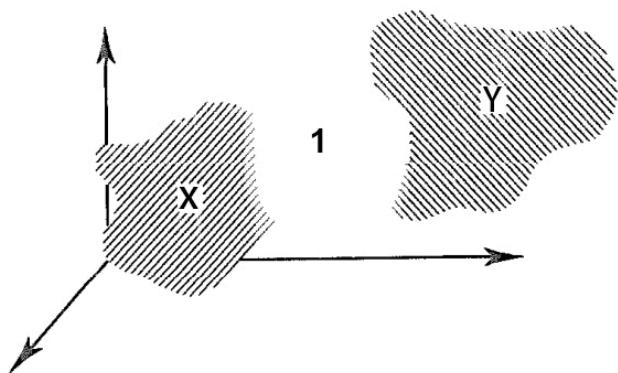


Free Energy Perturbation

Free energy perturbation (Staging)



$$\begin{aligned}\Delta A &= A(Y) - A(X) \\ &= [A(Y) - A(1)] - [A(X) - A(1)] \\ &= -k_B T \ln \left[\frac{Q(Y)}{Q(1)} \frac{Q(1)}{Q(X)} \right] \\ &= -k_B T \ln \left\langle -\frac{\mathcal{H}_Y - \mathcal{H}_1}{k_B T} \right\rangle_1 - k_B T \ln \left\langle -\frac{\mathcal{H}_1 - \mathcal{H}_X}{k_B T} \right\rangle_X\end{aligned}$$



$$\begin{aligned}\Delta A &= A(Y) - A(X) \\ &= [A(Y) - A(N)] + [A(N) - A(N-1)] + \dots \\ &\quad + [A(2) - A(1)] + [A(1) - A(X)] \\ &= -k_B T \ln \left[\frac{Q(Y)}{Q(N)} \frac{Q(N)}{Q(N-1)} \dots \frac{Q(2)}{Q(1)} \frac{Q(1)}{Q(X)} \right]\end{aligned}$$

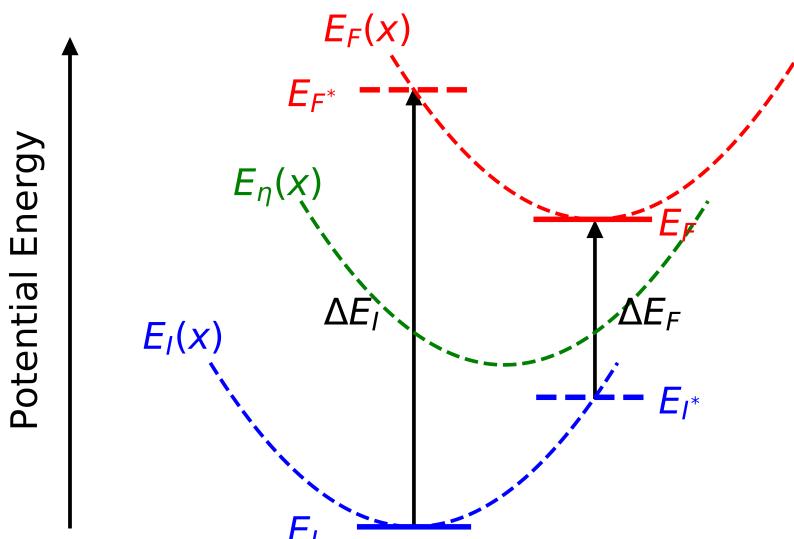
We are free to choose as many intermediate states as are necessary to get good overlaps and thus reliable value of the free energy difference.

Free Energy Perturbation

Potential energy (Classical Force Field):

$$v(\mathbf{r}^N) = \sum_{bonds} \frac{k_i}{2} (l_i - l_{i,0})^2 + \sum_{angles} \frac{k_\theta}{2} (\theta_i - \theta_{i,0})^2 + \sum_{torsions} \frac{V_n}{2} (1 + \cos(n\omega - \gamma)) \\ + \sum_{i=1}^N \sum_{j=i+1}^N (4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}})$$

$$E_\lambda(\mathbf{r}^N) = \lambda E_Y(\mathbf{r}^N) + (1 - \lambda) E_X(\mathbf{r}^N)$$



$$\Delta A = A(\lambda = 1) - A(\lambda = 0) = \int_0^1 d\lambda \frac{dA(\lambda)}{d\lambda}$$

$k_i = \lambda k_i(Y) + (1 - \lambda) k_i(X)$
$l_0 = \lambda l_0(Y) + (1 - \lambda) l_0(X)$
$k_\theta = \lambda k_\theta(Y) + (1 - \lambda) k_\theta(X)$
$\theta_0 = \lambda \theta_0(Y) + (1 - \lambda) \theta_0(X)$
$V_\omega = \lambda V_\omega(Y) + (1 - \lambda) V_\omega(X)$
$q_i = \lambda q_i(Y) + (1 - \lambda) q_i(X)$
$\epsilon = \lambda \epsilon(Y) + (1 - \lambda) \epsilon(X)$
$\sigma = \lambda \sigma(Y) + (1 - \lambda) \sigma(X)$

Thermodynamic Integration

$$\Delta A = -k_B T \ln \frac{Q_Y}{Q_X} = -k_B T \ln \frac{Q_{Y,NVT}^{excess}}{Q_{X,NVT}^{excess}}$$

$$\Delta A = \int_0^1 d\lambda \frac{dA(\lambda)}{d\lambda} = -k_B T \int_0^1 \left[\frac{\partial \ln Q_{NVT}^{excess}(\lambda)}{\partial \lambda} \right] d\lambda = \int_0^1 \frac{-k_B T}{Q_{NVT}^{excess}(\lambda)} \frac{\partial Q_{NVT}^{excess}(\lambda)}{\partial \lambda} d\lambda$$

|

$$Q_{NVT}^{excess} = \int d\mathbf{r}^N \exp\left[-\frac{E(\mathbf{r}^N)}{k_B T}\right]$$

$$\frac{\partial Q_{NVT}^{excess}(\lambda)}{\partial \lambda} = -\frac{1}{k_B T} \int d\mathbf{r}^N \frac{\partial E_\lambda(\mathbf{r}^N)}{\partial \lambda} \exp\left[-\frac{E_\lambda(\mathbf{r}^N)}{k_B T}\right]$$

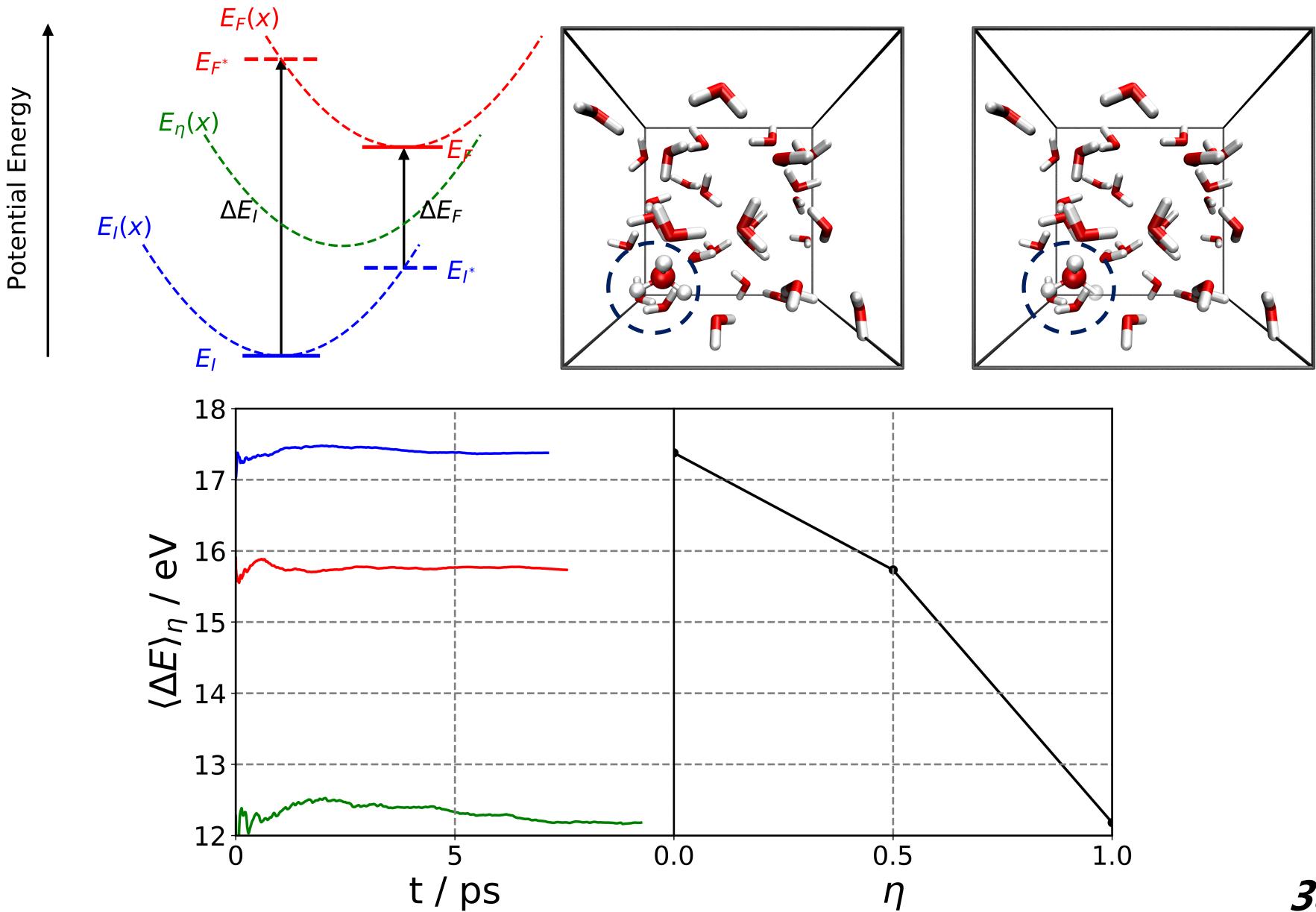
$$\frac{-k_B T}{Q_{NVT}^{excess}(\lambda)} \frac{\partial Q_{NVT}^{excess}(\lambda)}{\partial \lambda} = \frac{\int d\mathbf{r}^N \frac{\partial E_\lambda(\mathbf{r}^N)}{\partial \lambda} \exp\left[-\frac{E_\lambda(\mathbf{r}^N)}{k_B T}\right]}{\int d\mathbf{r}^N \exp\left[-\frac{E_\lambda(\mathbf{r}^N)}{k_B T}\right]} = \left\langle \frac{\partial E_\lambda}{\partial \lambda} \right\rangle_\lambda$$

↓

$$E_\lambda = \lambda E_Y + (1 - \lambda) E_X \quad \frac{\partial E_\lambda}{\partial \lambda} = E_Y - E_X = \Delta E$$

$$\Delta A = \int_0^1 d\lambda \left\langle \frac{\partial E_\lambda}{\partial \lambda} \right\rangle_\lambda = \int_0^1 d\lambda \langle \Delta E \rangle_\lambda$$

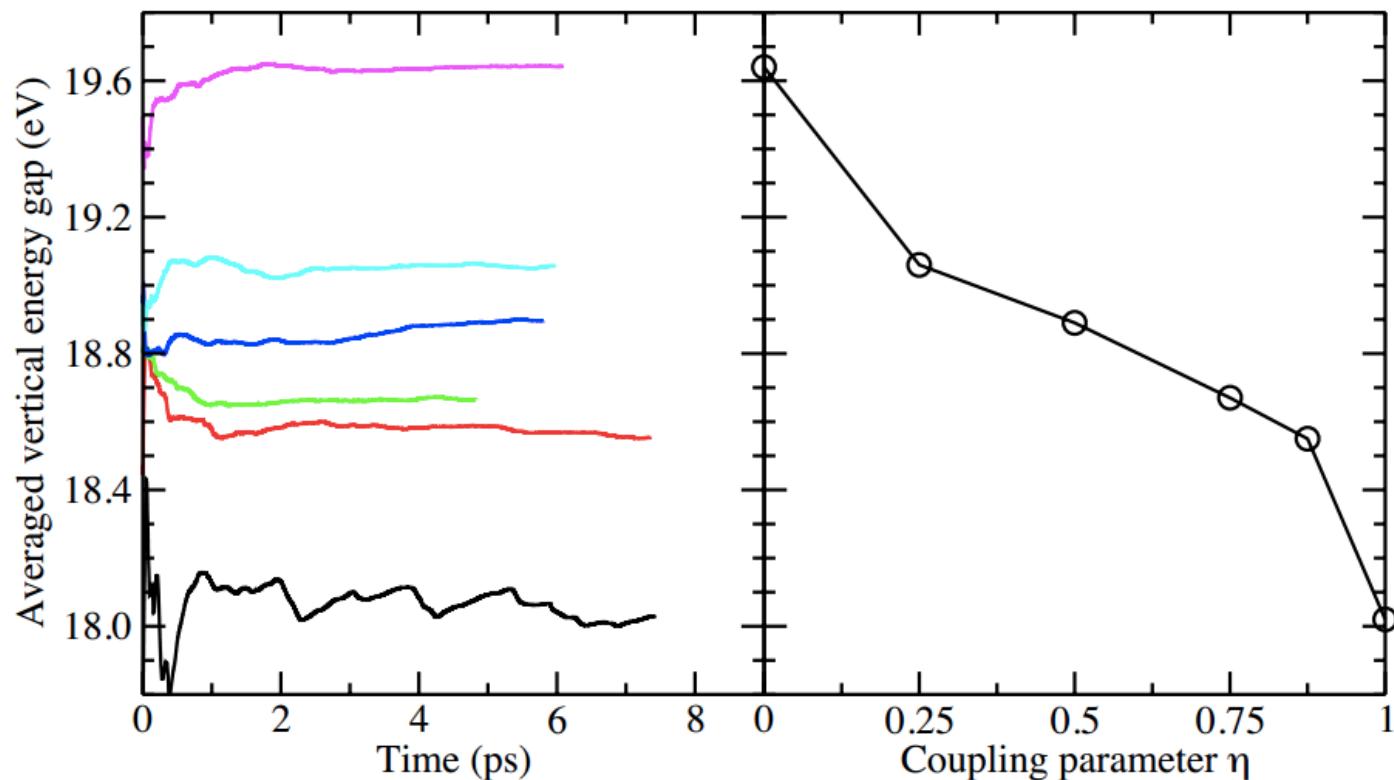
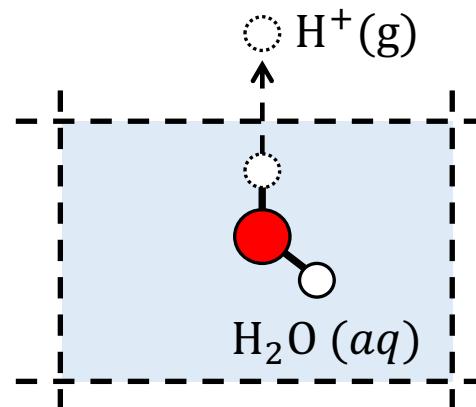
Thermodynamic Integration



pKa/Solvation Free Energy

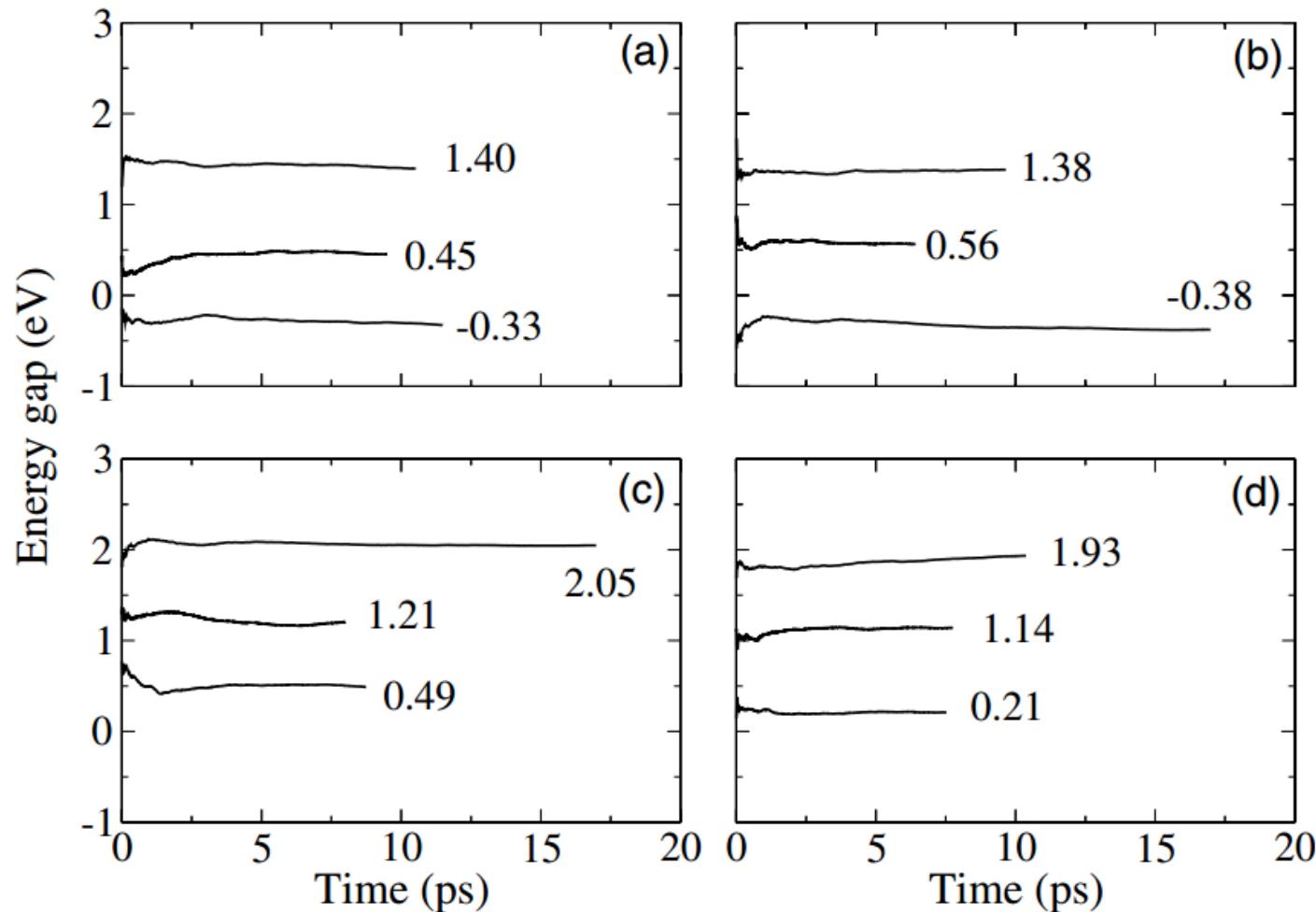
$$\Delta A = \int_0^1 d\lambda \left\langle \frac{\partial E_\lambda}{\partial \lambda} \right\rangle_\lambda = \int_0^1 d\lambda \langle \Delta E \rangle_\lambda$$

“Alchemical Transformation”



Redox Potential

$$\Delta A = \int_0^1 d\lambda \left\langle \frac{\partial E_\lambda}{\partial \lambda} \right\rangle_\lambda = \int_0^1 d\lambda \langle \Delta E \rangle_\lambda \quad Q(aq) + e^-(\text{vac.}) \rightarrow Q^-(aq)$$



Further Readings

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4. Frenkel D. and Smit B. *Understanding molecular simulation: from algorithms to applications*. Elsevier, 2nd edn, 2002.
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