Understanding Molecular Simulation

Advanced MC

Advanced MC Sampling

- Exotic ensembles
- Improved sampling:
  - Rejectionless cluster moves
  - include rejections: waste recycling
- Computing the chemical potential
  - Widom insertion
  - overlapping distributions
- Biased sampling: umbrella sampling
- The problem of computer time

Summary ensembles

Ensemble	Constant (Imposed)	Fluctuating (Measured)	Function
NVT	N,V,T	P	$\beta F=-\ln Q(N,V,T)$
NPT	N,P,T	V	$\beta G=-\ln Q(N,P,T)=\beta F+\beta PV$
μVT	μ,V,T	N	$\beta \Omega =-\ln Q(\mu,V,T)=-\beta PV$

Semi grand ensemble

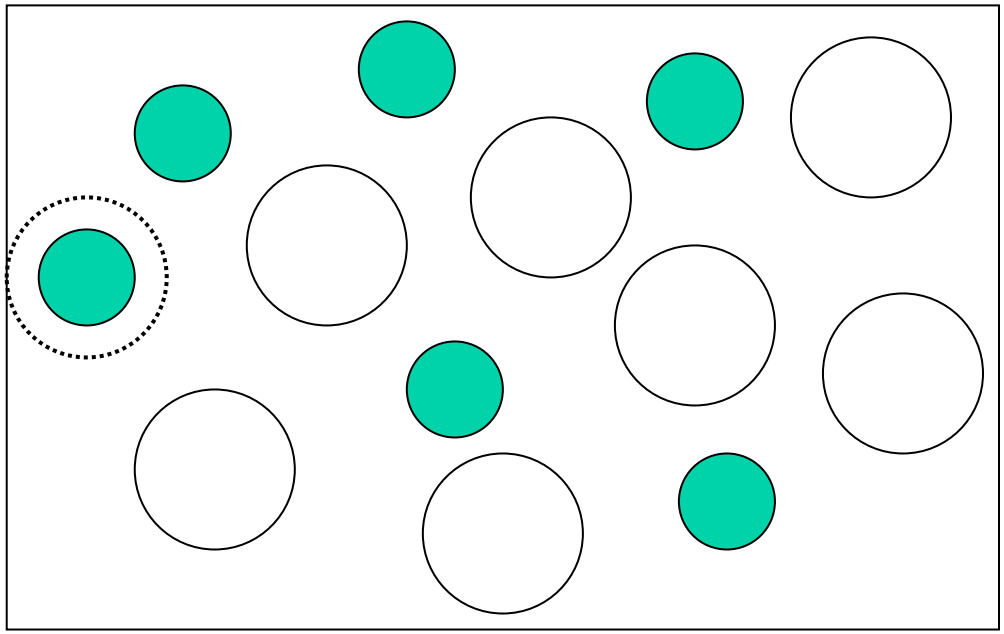
- For mixtures an additional ensemble exists: semigrand
- Constant NΔμVT or NΔμPT :
  - The difference between the chemical potentials of the components is fixed
  - total number of particles is fixed
  - Pressure or volume fixed

- For a binary mixture
  - N_1, N_2 are allowed to change, but $N_1+N_2=N$
  - μ_2, μ_1 are allowed to change, but $\Delta\mu = \mu_2 - \mu_1$

$$\Xi = \frac{\beta P}{N!\Lambda^{3N}} \int dV V^N \exp[-\beta PV] \times \sum_{identities} \exp[\beta N_2 \Delta\mu] \times \int ds^N \exp[-\beta U(s^N)]$$

In binary mixture just 1,2

MC move changes identity



$$P_{acc}(1 \rightarrow 2) = \min[1, \exp[-\beta U + \beta \Delta \mu]$$

Advantage: at high densities still good acceptance

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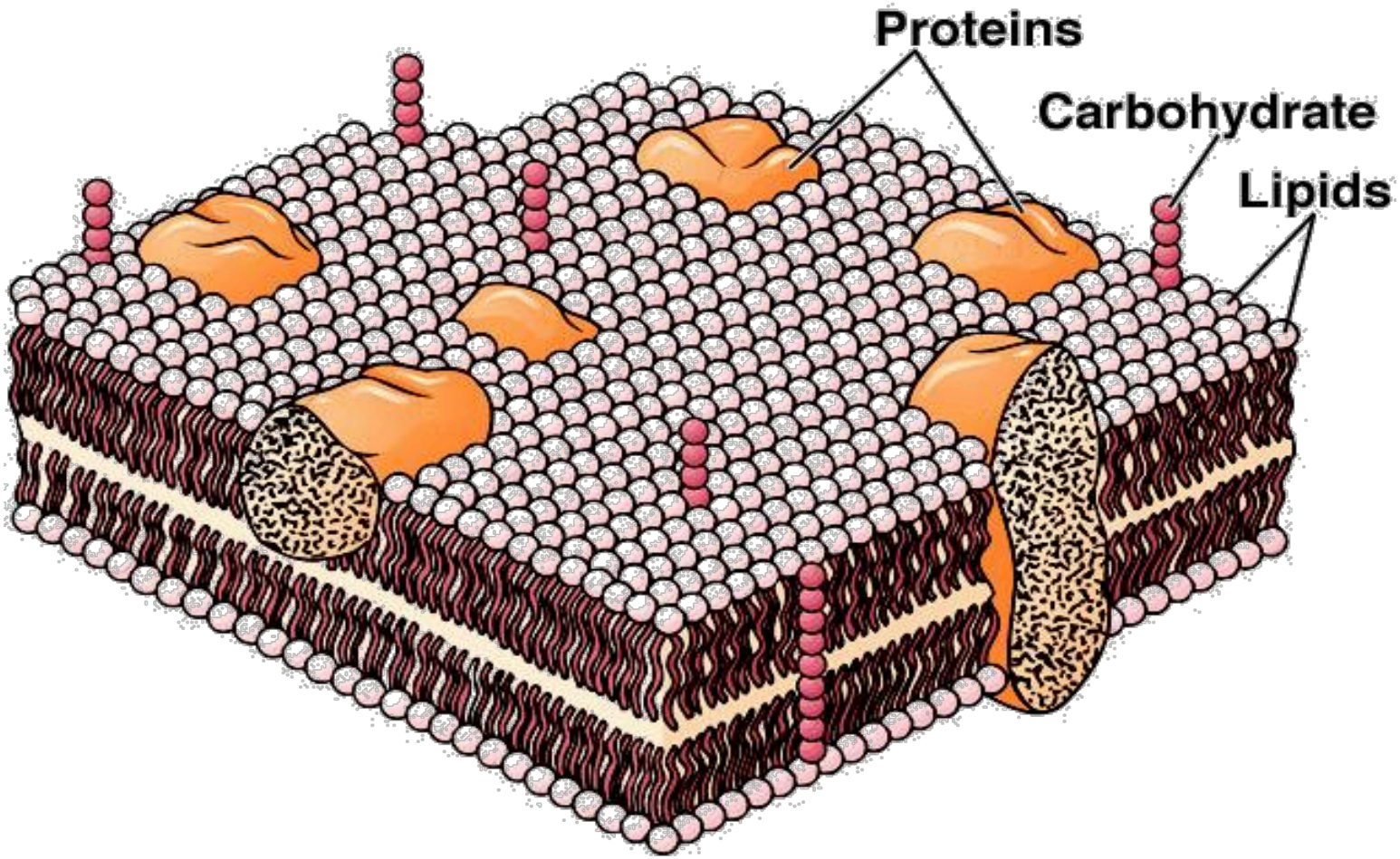
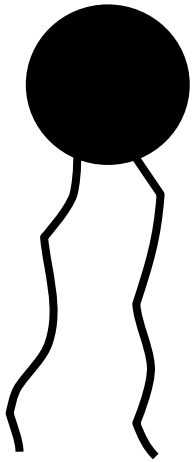
NVT	N,V,T	P	$\beta F=-\ln Q(N,V,T)$
NPT	N,P,T	V	$\beta G=-\ln Q(N,P,T)=\beta F+\beta PV$
μVT	μ,V,T	N	$\beta \Omega =-\ln Q(\mu,V,T)=-\beta PV$
ΔμVT	ΔμVT	μ_i ,N_i	$\beta Y=-\ln \Xi(\Delta\mu,V,T)$

Exotic ensembles

What to do with a biological membrane?

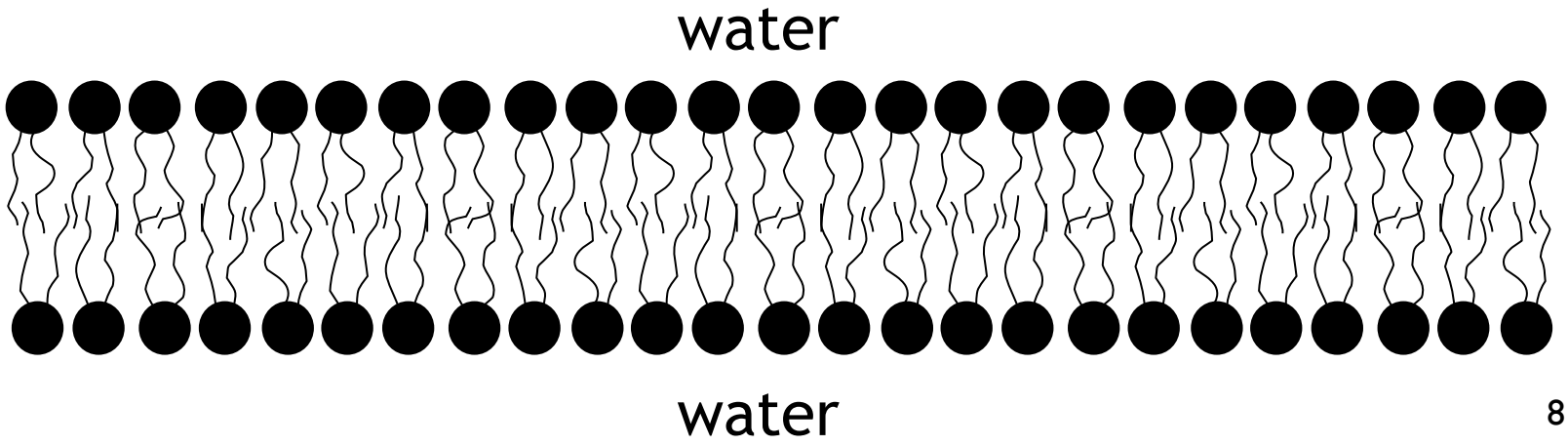


Model membrane: Lipid bilayer



hydrophilic head group

two hydrophobic tails

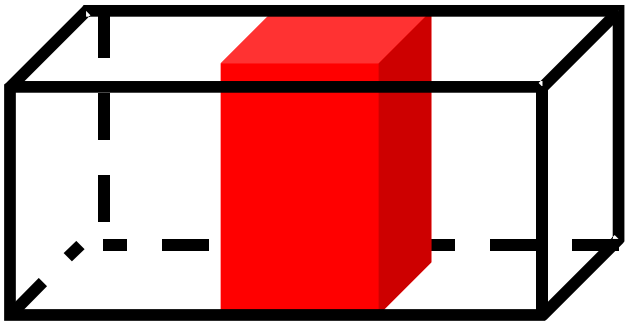


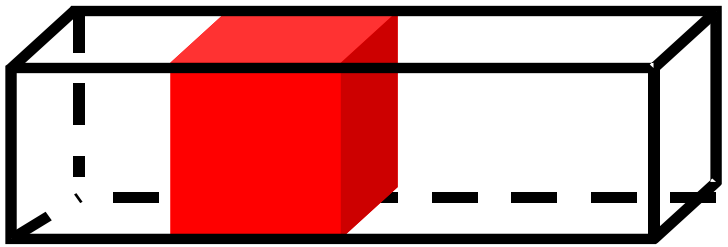
Surface Tension γ controls area per lipid

$\gamma<0$	compressed bilayer
$\gamma=0$	tensionless bilayer
$\gamma>0$	stretched bilayer

Simulations at imposed surface tension

- Simulation to a constant surface tension
  - Simulation box: allow the area of the bilayer to change in such a way that the volume is constant.





Constant surface tension simulation

$$N_{N\gamma T}\left(A,\mathbf{r}^N\right) \propto \exp[-\beta(\mathrm{U}(\mathbf{r}^N)-\gamma\,\mathrm{A})]$$

A ➡ A’

L ➡ L’

A L = A’ L’ = V

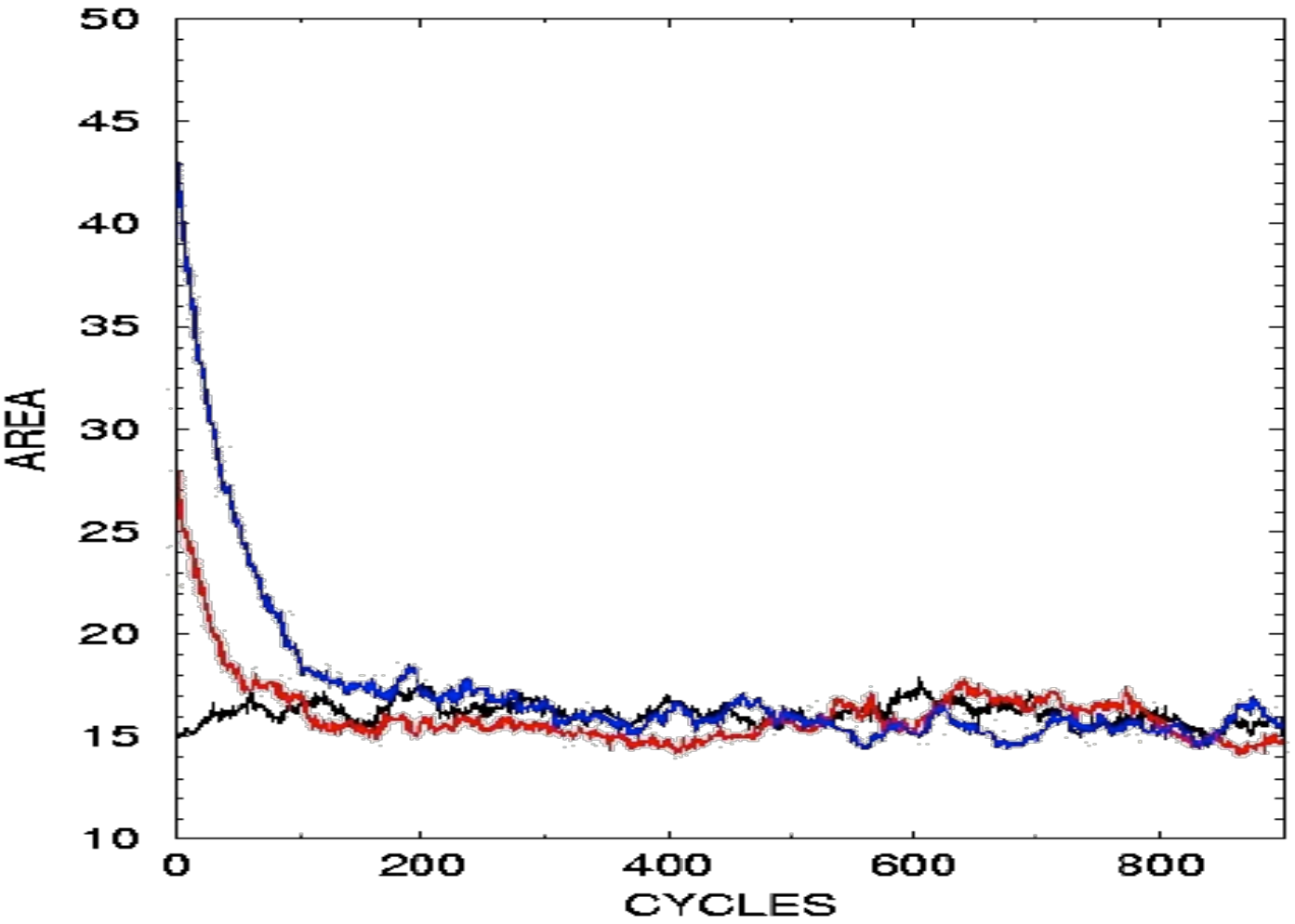
$$P_{acc} = \min(1,\exp\{-\beta[\mathrm{U}(\mathbf{s}^N;\mathrm{A}')-\mathrm{U}(\mathbf{s}^N;\mathrm{A})-\gamma(\mathrm{A}'-\mathrm{A})]\})$$

Tensionless state: γ= 0

$\gamma(A_o)$ = -0.3 +/- 0.6

$\gamma(A_o)$ = 2.5 +/- 0.3

$\gamma(A_o)$ = 2.9 +/- 0.3



Advanced MC Sampling

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Conventional MC performs a random walk in configuration space, such that the number of times that each point is visited, is proportional to its Boltzmann weight.

$$n(\mathbf{r}^N) = c \exp[-\beta \mathcal{U}(\mathbf{r}^N)]$$

$$\frac{\mathrm{acc}(o \to n)}{\mathrm{acc}(n \to o)} = \frac{\mathcal{N}(n)}{\mathcal{N}(o)} = \exp\{-\beta[\mathcal{U}(n) - \mathcal{U}(o)]\}$$

Metropolis,
Rosenbluth,Rosenbluth,

Teller and Teller choice:

$$\mathrm{acc}(o \to n) = \min\left(1, \exp\{-\beta[\mathcal{U}(\mathbf{r}'^N) - \mathcal{U}(\mathbf{r}^N)]\}\right)$$

Satisfactory?


MAXWELL DEMONS ON STRIKE
100 % NO LESS!
ACCEPT OUR MOVES NOW!!

Solution of conflict: play with the a-priori probabilities of trial moves:

$$\alpha(o \to n) \neq \alpha(n \to o)$$

$$\frac{\mathsf{acc}(o \to n)}{\mathsf{acc}(n \to o)} = \frac{\alpha(n \to o)}{\alpha(o \to n)} \exp\{-\beta[\mathcal{U}(n) - \mathcal{U}(o)]\}.$$

In particular, if:

$$\frac{\alpha(n \to o)}{\alpha(o \to n)} = \exp\{-\beta[\mathcal{U}(o) - \mathcal{U}(n)]\}.$$

Then

$$\frac{\mathsf{acc}(o \to n)}{\mathsf{acc}(n \to o)} = 1 \qquad \text{(100\% acceptance)}$$

100% acceptance can be achieved in special cases: e.g. Swendsen-Wang, Wolff, Luyten, Whitelam-Geissler, Bortz-Kalos-Lebowitz…

General idea: construct “cluster moves”

Simplest example: Swendsen-Wang

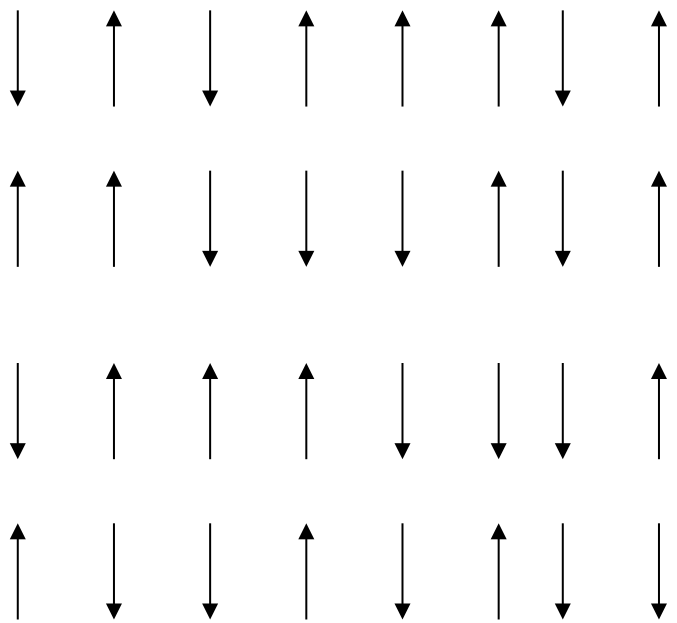
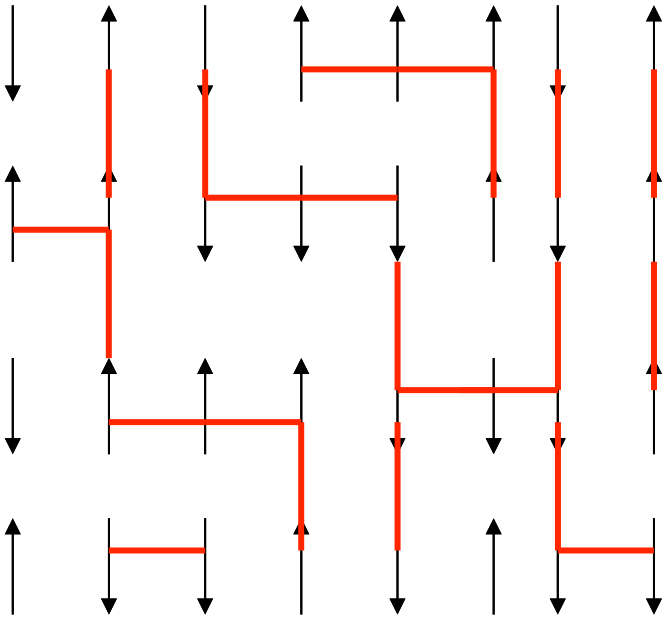


Illustration: 2D Ising model.

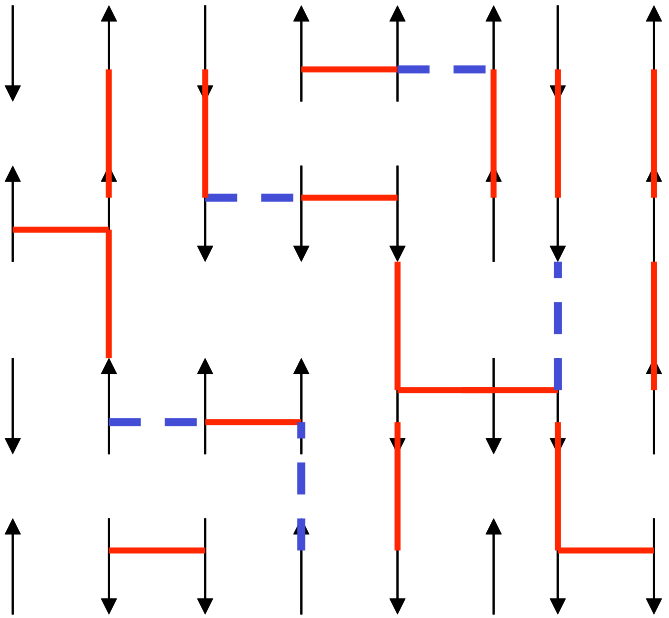
Snapshot: some neighbors are parallel, others anti-parallel



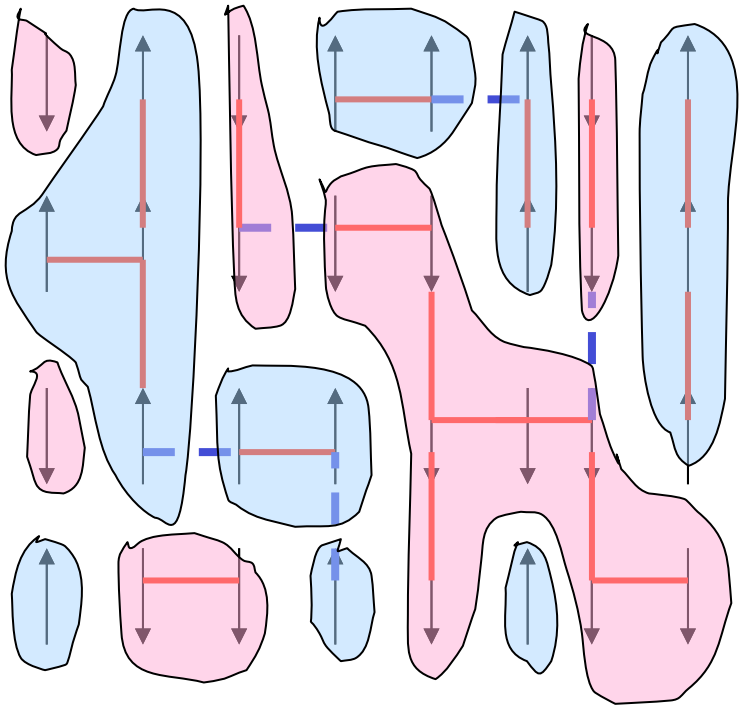
Number of parallel nearest-neighbor pairs: $\mathbf{N_p}$

Number of anti-parallel nearest neighbor pairs is: $\mathbf{N_a}$

Total energy: $\mathbf{U = (N_a - N_p)\, J}$

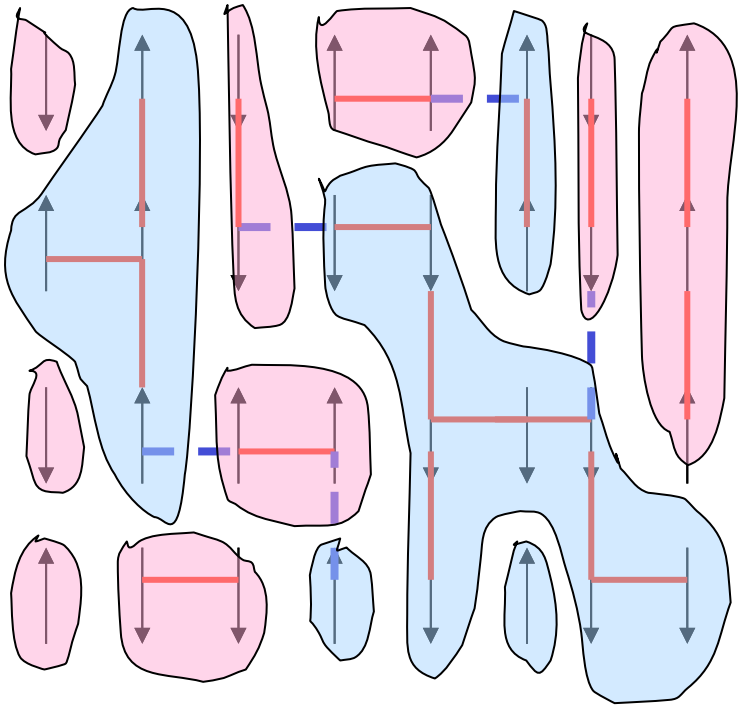


Make “bonds” between parallel neighbors. The probability to have a bond (red line) between parallel neighbors is **p** (as yet undetermined). With a probability **1-p**, parallel neighbors are not connected (blue dashed line).



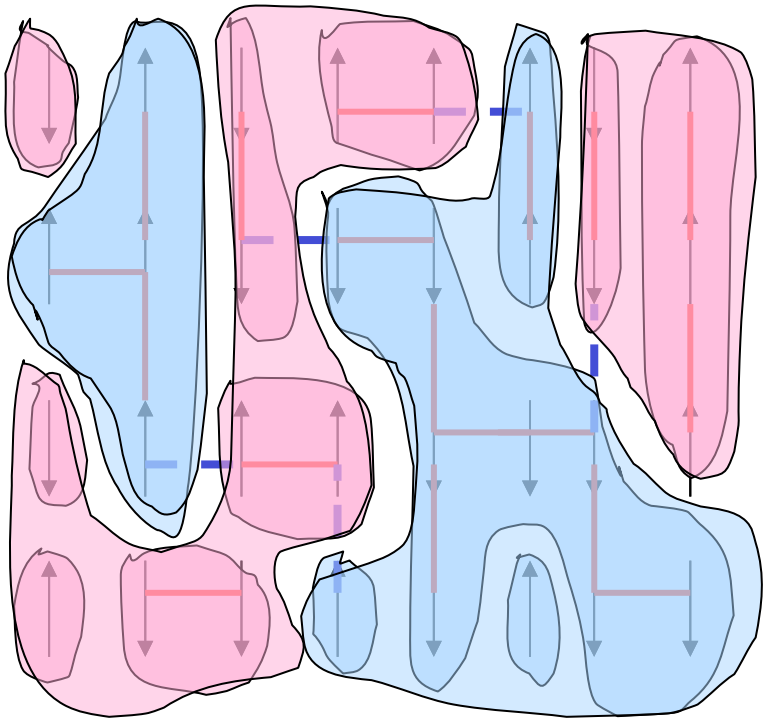
Form clusters of all spins that are connected by bonds. Some clusters are all “spin up” others are all “spin down”.

Denote the number of clusters by **M**.

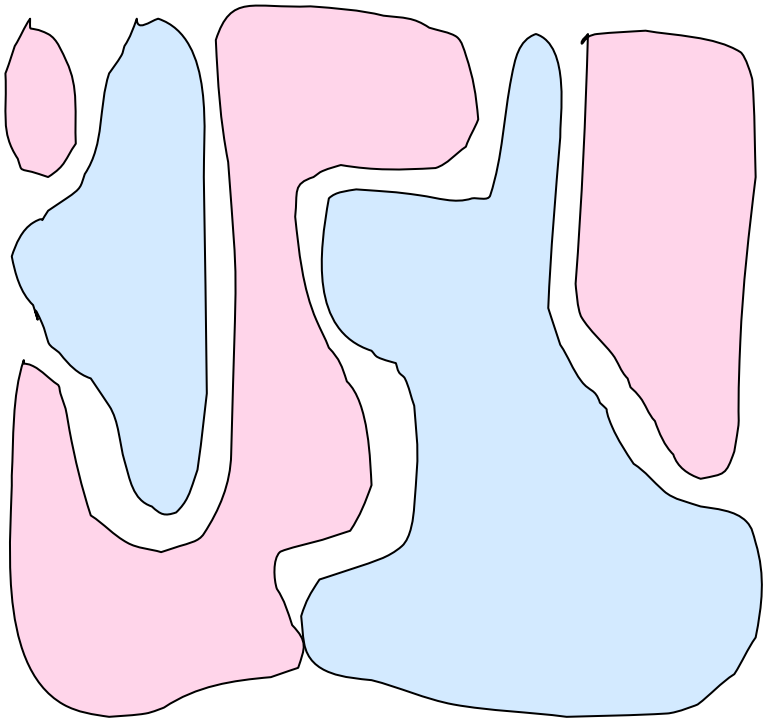


Now randomly flip clusters. This yields a new cluster configuration with probability $\mathbf{P_{(flip)} = (1/2)^M}$.

Then reconnect parallel spins



Next: forget about the “bonds”…



New spin configuration!

$$P_o P_{clus}(o) P_{flip}(M) P_{acc}(o \to n)$$

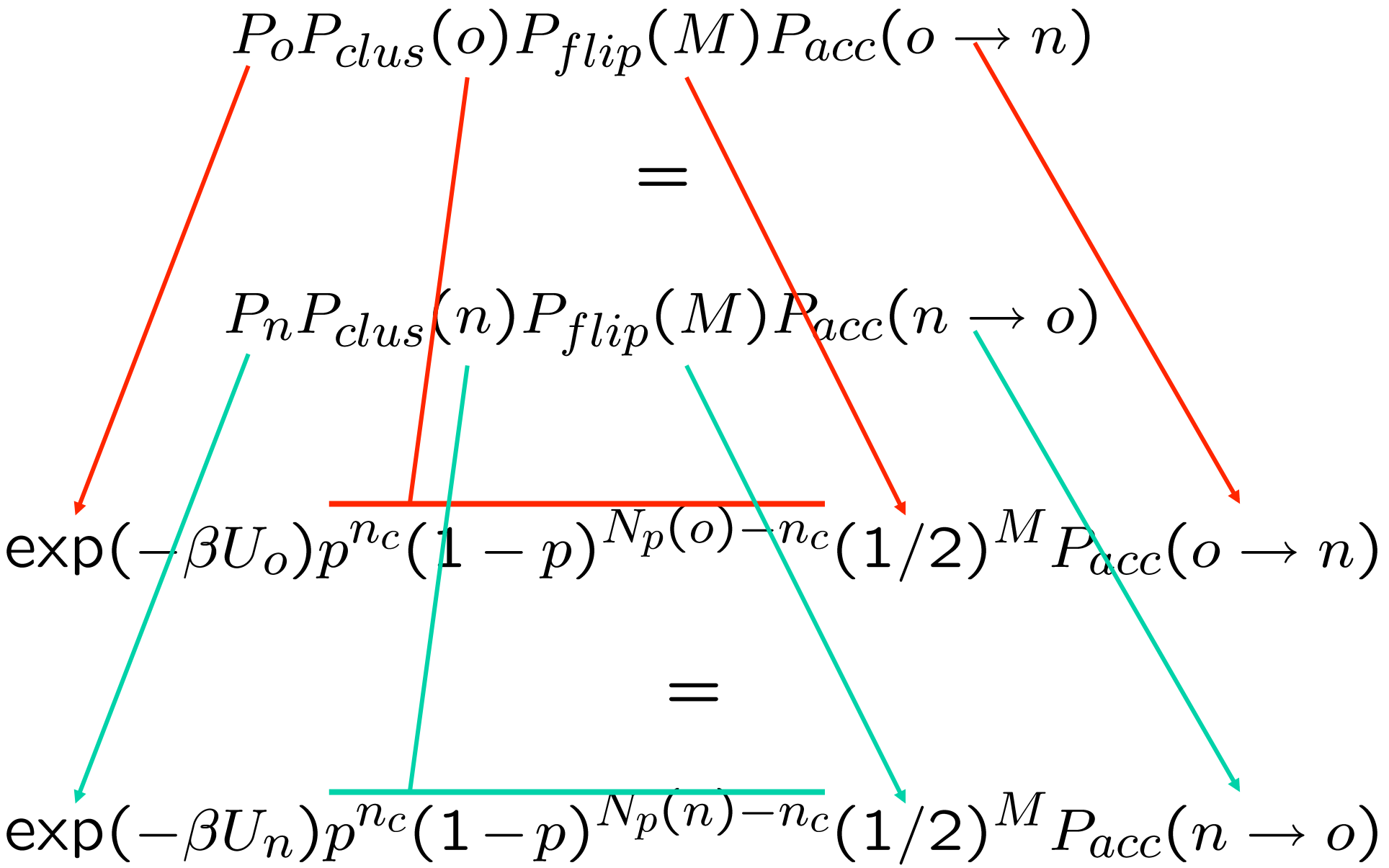
$$=$$

$$P_n P_{clus}(n) P_{flip}(M) P_{acc}(n \to o)$$

$$\exp(-\beta U_o) p^{n_c} (1-p)^{N_p(o)-n_c} (1/2)^M P_{acc}(o \to n)$$

$$=$$

$$\exp(-\beta U_n) p^{n_c} (1-p)^{N_p(n)-n_c} (1/2)^M P_{acc}(n \to o)$$


$P_o P_{clus}(o) P_{flip}(M) P_{acc}(o \to n)$
=
$P_n P_{clus}(n) P_{flip}(M) P_{acc}(n \to o)$
$\exp(-\beta U_o) p^{n_c} (1-p)^{N_p(o)-n_c} (1/2)^M P_{acc}(o \to n)$
=
$\exp(-\beta U_n) p^{n_c} (1-p)^{N_p(n)-n_c} (1/2)^M P_{acc}(n \to o)$

Moreover, we want 100% acceptance, i.e.:

$$\mathbf{P_{acc}(o \to n) = P_{acc}(n \to o) = 1}$$

$$\exp(-\beta U_o) p^{n_c} (1-p)^{N_p(o)-n_c} (1/2)^M P_{acc}(o \to n)$$

$$=$$

$$\exp(-\beta U_n) p^{n_c} (1-p)^{N_p(n)-n_c} (1/2)^M P_{acc}(n \to o)$$

Hence:

$$\exp(-\beta U_o)(1-p)^{N_p(o)} = \exp(-\beta U_n)(1-p)^{N_p(n)}$$

$$\exp(\beta(U_n - U_o)) = (1-p)^{N_p(n)-N_p(o)}$$

But remember:

$$U_n - U_o = J(N_a(n) - N_p(n)) - J(N_a(o) - N_p(o))$$

or

$$\Delta U = J(\Delta N_a - \Delta N_p)$$

But: $\Delta N_a = -\Delta N_p$

and therefore

$$\Delta U = -2J\Delta N_p$$

$$\exp(\beta(U_n - U_o)) = \exp(-2\beta J(N_p(n) - N_p(o)))$$

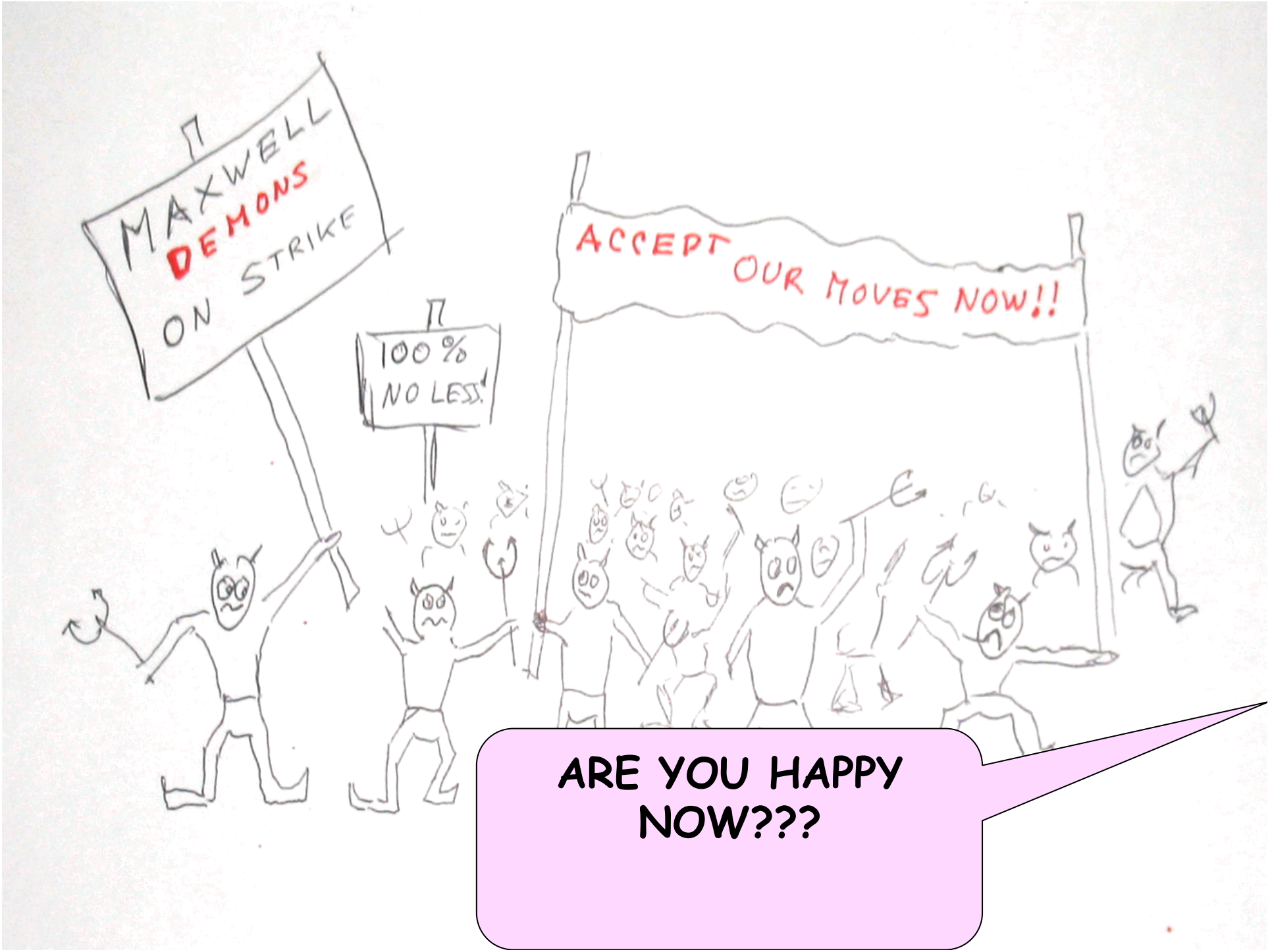
Combining this with:

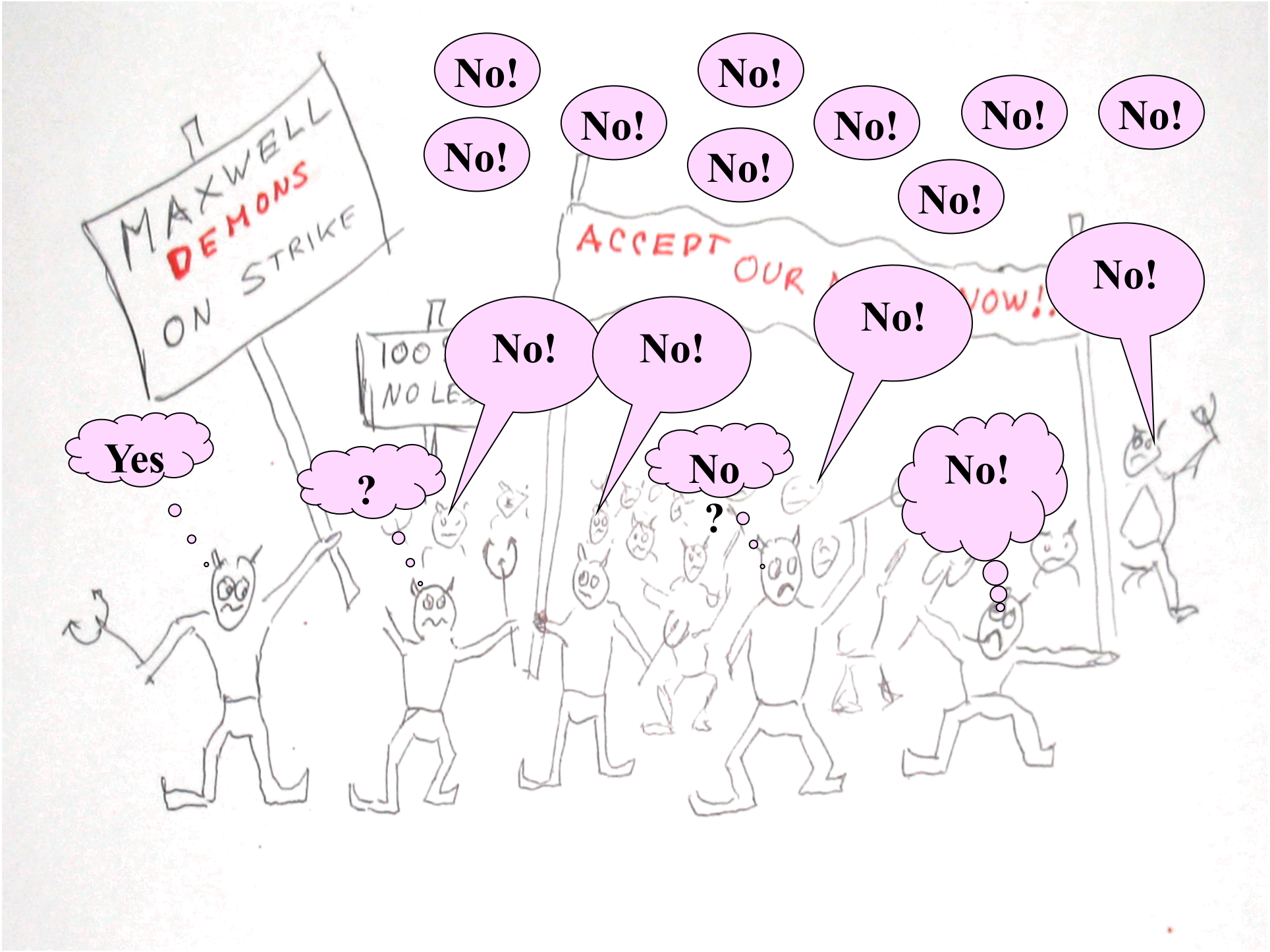
$$\exp(\beta(U_n - U_o)) = (1-p)^{N_p(n)-N_p(o)}$$

we obtain:

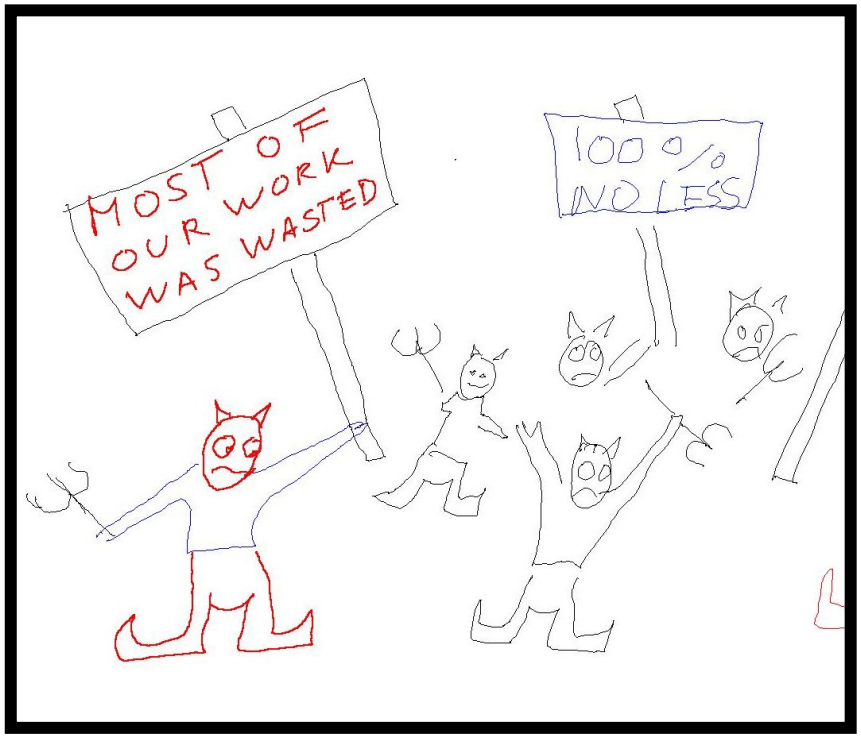
$$p = 1 - \exp(-2\beta J)$$

100% acceptance!!!


MAXWELL DEMONS ON STRIKE
100 % NO LESS!
ACCEPT OUR MOVES NOW!!
ARE YOU HAPPY NOW???


MAXWELL
DEMONS
ON STRIKE
ACCEPT
No!
No!
No!
No!
No!
No!
No!
No!
No!
No!
No!
No!
No!
Yes
?
No
?
No!

Why not?



For Swendsen-Wang, we generate very many trial states : with **n** clusters, $\mathbf{2^n}$ possible states…)

…and yet we accept only **one**!

HERETICAL MC SAMPLING

Include "rejected" moves in the sampling

Why is this heretical?:

Metropolis "importance" sampling is **based** on the earlier (Ulam/von Neumann) **rejection** method applied to **random** MC sampling

This is the key:

$$\sum_m \rho(m)\pi_{mn} = \rho(n)$$

The transition matrix π leaves the equilibrium distribution ρ unchanged.

$$\langle A \rangle_\rho = \sum_n A_n \rho_n$$

we can rewrite this using $\sum_m \rho_m \pi_{mn} = \rho_n$

$$\sum_n A_n \rho_n = \sum_n \sum_m A_n \rho_m \pi_{mn} = \sum_m \rho_m \sum_n A_n \pi_{mn}$$

$$= \sum_m \rho_m \sum_n A_n \pi_{mn} \Leftrightarrow \langle A \rangle_\rho = \left\langle \sum_n \pi_{mn} A_n \right\rangle_{\rho_m}$$

$$\langle A \rangle_\rho = \left\langle \sum_n \pi_{mn} A_n \right\rangle_{\rho_m}$$

Note that <A> is no longer an average over “visited” states – we also include “rejected” moves in the sampling.

$$\langle A \rangle_\rho = \left\langle \sum_n \pi_{mn} A_n \right\rangle_{\rho_m}$$

This relation also holds for any set of "connected" trial states: i.e. the possible final states of a single (decent) MC trial move.

$$\langle A \rangle_\rho = \left\langle \sum_n \pi_{mn} A_n \right\rangle_{\rho_m}$$

For instance: in conventional MC, there would be only two states (the “old” state and the “new” state)

$$\langle A \rangle_\rho = \left\langle \sum_n \pi_{mn} A_n \right\rangle_{\rho_m}$$

But in other algorithms, there are many. e.g. in the Swendsen-Wang algorithm: **n** clusters that can be flipped $\Rightarrow$ $\mathbf{2^n}$ connected states.

The more parallel the algorithm, the better…

$$\langle A \rangle_\rho = \left\langle \sum_n \pi_{mn} A_n \right\rangle_{\rho_m}$$

Note that the transition matrix that is used in the averaging need not be the same as the one used in sampling the ρ_m.

(e.g. one could be "Barker" and the other "Metropolis")

$$\langle A \rangle_\rho = \left\langle \sum_n \pi_{mn} A_n \right\rangle_{\rho_m}$$

How to sample this?

$$\pi_{nm} = \alpha_{nm} P_{acc}(nm)$$

$$\langle A \rangle_\rho = \sum_m \rho_m \left\langle \sum_n P_{acc}(mn) A_n \right\rangle_\alpha$$

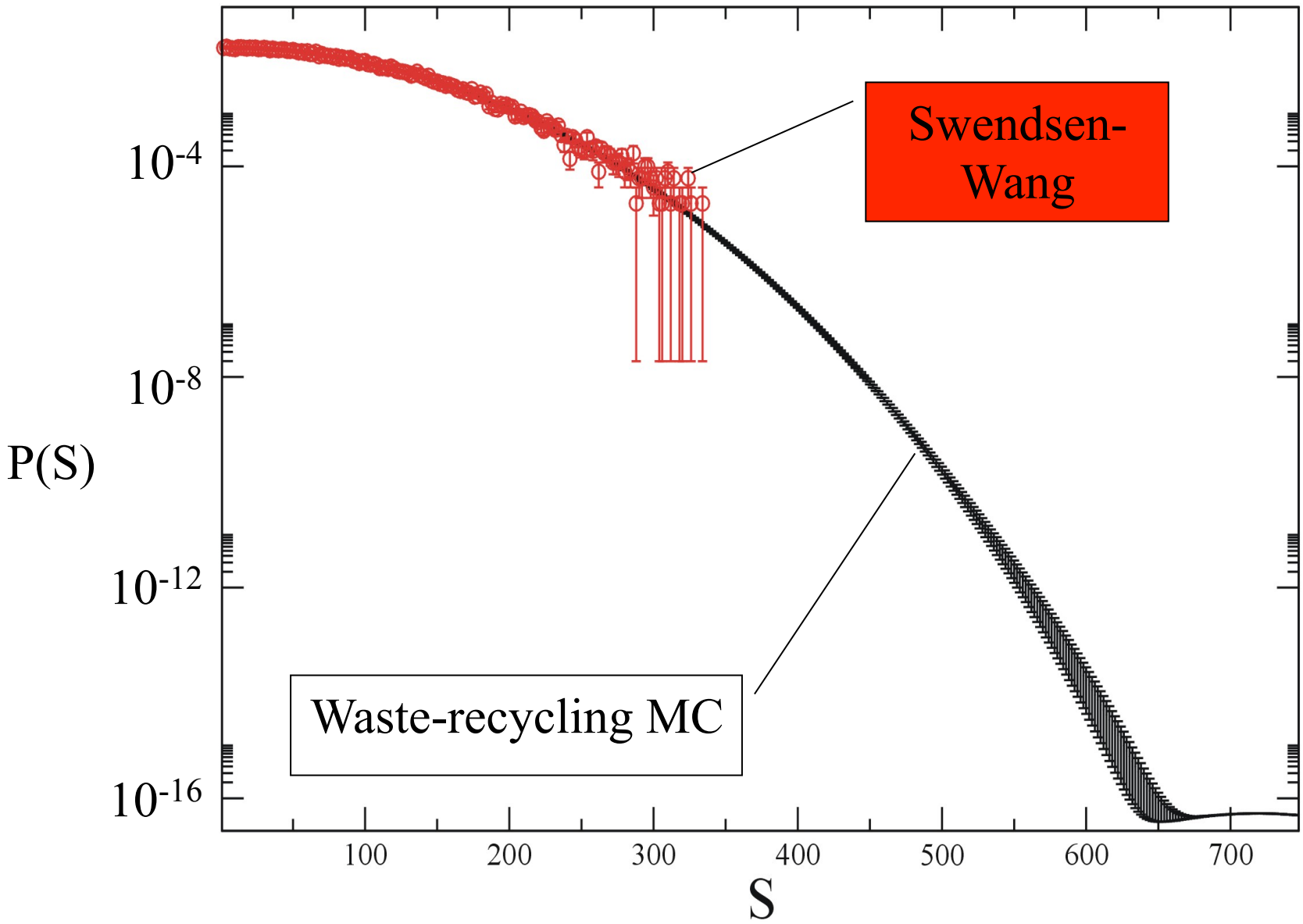
Slightly dishonest and slightly trivial example:

Sampling the magnetization of a 2D Ising system

Compare:

1. Normal (Swendsen-Wang) MC
   (sample **one** out of 2^n states)

2. Idem + "waste
   recycling" (sample **all** 2^n states)


Swendsen-
Wang
Waste-recycling MC
P(S)
10-4
10-8
10-12
10-16
100
200
300
400
500
600
700
S

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- Improved sampling:
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- **Computing the chemical potential**
  - **Widom insertion**
  - **overlapping distributions**

- Biased sampling: umbrella sampling

- The problem of computer time

A central quantity in the study of (phase) equilibria is the chemical potential μ.

We have an “intuitive” picture of the temperature T and the pressure P.

Can we gain a similar “intuitive” understanding of the chemical potential?

First, look at the formal definition:

$$
\begin{aligned}
dE &= TdS - PdV + \mu dN \\
dF &= -SdT - PdV + \mu dN
\end{aligned}
$$

Hence:

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{S,V} = \left(\frac{\partial F}{\partial N}\right)_{T,V}$$

Using $F=-k_B T \ln Q(N,V,T)$ we can write:

$$\begin{aligned}
\mu &= \left(\frac{\partial F}{\partial N}\right)_{V,T} \\
&= -k_B T \lim_{\Delta N \to 0} \frac{\ln Q(N+\Delta N, V, T) - \ln Q(N, V, T)}{\Delta N} \\
&= -k_B T \ln \left(\frac{Q(N+1, V, T)}{Q(N, V, T)}\right)_{V,T}
\end{aligned}$$

For N >> 1

Example: ideal gas

$$Q(N,V,T) = \frac{V^N}{\Lambda^{3N} N!}$$

$$\begin{aligned}
\mu &= \lim_{N\to\infty} -k_B T \ln \left[\frac{\frac{V^{N+1}}{\Lambda^{3(N+1)}(N+1)!}}{\frac{V^N}{\Lambda^{3N} N!}} \right] \\
&= -k_B T \ln \frac{V}{\Lambda^3 (N+1)} \\
&\approx k_B T \ln \left(\Lambda^3 \rho \right)
\end{aligned}$$

with ρ ≡ (N/V)

The ideal-gas result, we had obtained before.
Now, with interacting particles:

$$\mu = \lim_{N\to\infty} -k_B T \ln\left[\frac{Q(N+1,V,T)}{Q(N,V,T)}\right]$$
$$\equiv \mu^{\mathrm{id}} + \mu^{\mathrm{excess}}$$

We can there write the “excess” part of the chemical potential as:

$$\mu^{\mathrm{ex}} = k_B T\left[\ln\frac{Q(N+1,V,T)}{Q(N,V,T)} - \ln\left(\frac{V^3}{\Lambda^3(N+1)}\right)\right]$$
$$= k_B T \ln\left[\frac{Q(N+1,V,T)\Lambda^3(N+1)}{VQ(N,V,T)}\right]$$

Now we use the explicit expression for Q(N,V,T):

$$Q(N,V,T) = \frac{1}{\Lambda^{3N}N!}\int d\mathbf{r}^N e^{-\beta U(\mathbf{r}^N)}$$

$$\mu^{\text{ex}} = -k_B T \ln \left(\frac{\int d\mathbf{r}^{N+1} e^{-\beta U(\mathbf{r}^{N+1})}}{V \int d\mathbf{r}^{N} e^{-\beta U(\mathbf{r}^{N})}} \right)$$

We define:

$$\Delta U(\mathbf{r}^N; \mathbf{r}_{N+1}) \equiv U(\mathbf{r}^{N+1}) - U(\mathbf{r}^N)$$

Then

$$\begin{aligned} \mu^{\text{ex}} &= -k_B T \ln \left(\frac{\int d\mathbf{r}^{N+1} e^{-\beta \left[U(\mathbf{r}^N) + \Delta U(\mathbf{r}^N; \mathbf{r}_{N+1}) \right]}}{V \int d\mathbf{r}^{N} e^{-\beta U(\mathbf{r}^N)} } \right) \\ &= -k_B T \ln \left(\frac{1}{V} \int d\mathbf{r}_{N+1} \frac{\int d\mathbf{r}^{N} e^{-\beta \left[U(\mathbf{r}^N) + \Delta U(\mathbf{r}^N; \mathbf{r}_{N+1}) \right]}}{\int d\mathbf{r}^{N} e^{-\beta U(\mathbf{r}^N)}} \right) \end{aligned}$$

$$\begin{aligned}\mu^{\mathrm{ex}} &= -k_B T \ln\left(\frac{1}{V}\int d\mathbf{r}_{N+1}\frac{\int d\mathbf{r}^N e^{-\beta U(\mathbf{r}^N)} e^{-\beta\Delta U(\mathbf{r}^N;\mathbf{r}_{N+1})}}{\int d\mathbf{r}^N e^{-\beta U(\mathbf{r}^N)}}\right) \\ &= -k_B T \ln\frac{1}{V}\int d\mathbf{r}_{N+1}\left\langle e^{-\beta\Delta U(\mathbf{r}^N;\mathbf{r}_{N+1})}\right\rangle_N\end{aligned}$$

For a homogeneous system, the average does not depend on the position $\mathbf{r}_{N+1}$. Hence

$$\beta\mu^{\mathrm{ex}} = -\ln\left\langle e^{-\beta\Delta U}\right\rangle_N$$

In words: the excess chemical potential is equal to minus the logarithm of the average Boltzmann factor associated with the **random insertion** of an additional particle N+1 in an N-particle system.

So, finally, we get:

$$\mu = \mu_{id.gas} - kT \ln \left(\int ds_{N+1} \langle \exp(-\beta \Delta U(s_{N+1}, s^N) \rangle \right)$$

Interpretation:

1. Evaluate ΔU for a random insertion of a molecule in a system containing N molecule.
2. Compute $\exp(-\beta \Delta U)$
3. Repeat M times and compute the average "Boltzmann factor" $< \exp(-\beta \Delta U) >$
4. Then $\mu_{excess} = -kT \ln < \exp(-\beta \Delta U) >$

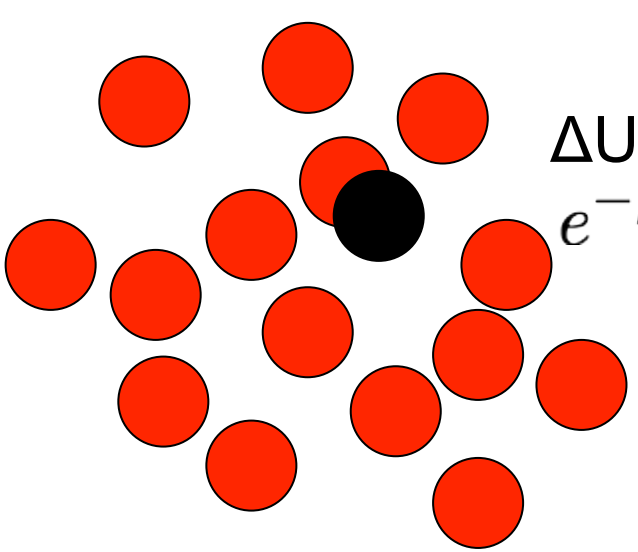
Algorithm 16 (Widom Test Particle Insertion)

```
 subroutine Widom                    excess chemical potential
                                     via the addition of test particles
 xtest=box*ranf()                    generate a random position
 call ener(xtest,entest)             determine energy
 wtest=wtest                         update Boltzmann factor in (7.2.5)
+       +exp(-beta*entest)
 return
 end
```

This method to evaluate μ is commonly known as **Widom**'s "particle-insertion method".

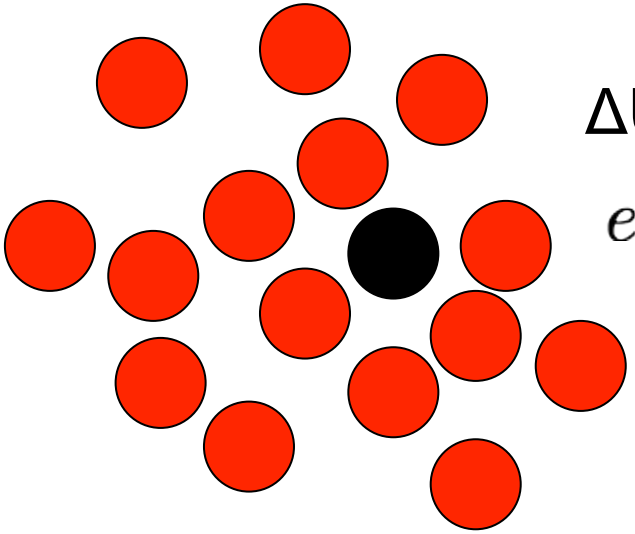
Ben Widom

Example: excess chemical potential of "hard" particles



ΔU=∞

$$e^{-\beta \Delta U} = 0$$



ΔU=0

$$e^{-\beta \Delta U} = 1$$

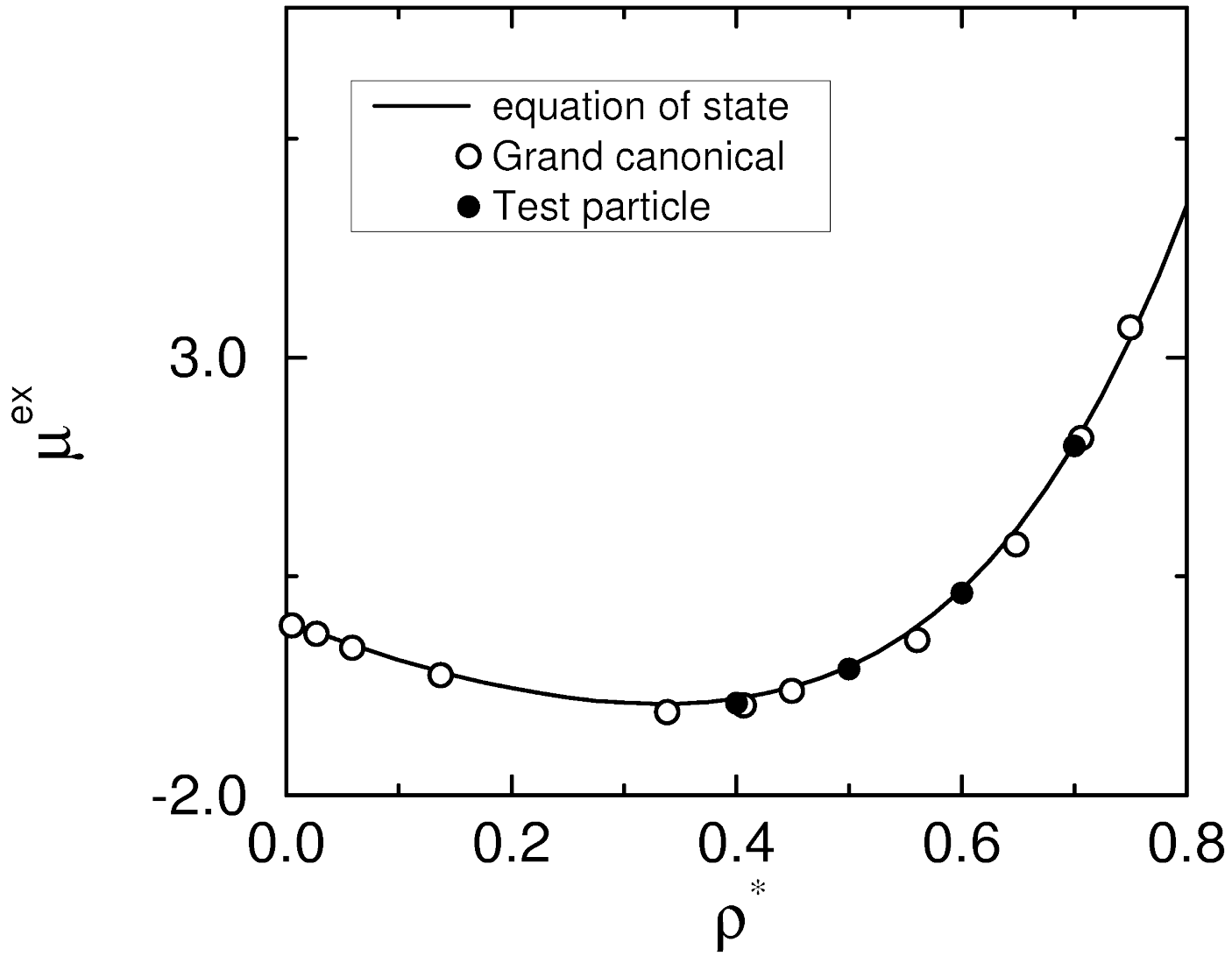
$$\begin{aligned}\left\langle e^{-\beta \Delta U} \right\rangle &= P_{\text{overlap}} \times 0 + P_{\text{no overlap}} \times 1 \\ &= P_{\text{no overlap}}\end{aligned}$$

In the case of hard particles, the excess chemical potential is related to the probability of a successful random insertion:

$$\beta \mu^{\text{ex}} = -k_B T \ln P_{\text{no overlap}}$$

Example of an application:
We can use the particle-insertion method to derive an expression for the second virial coefficient.

Lennard-Jones fluid



Other ensembles: NPT

NVT: Helmholtz free energy

$$\mu \equiv \left(\frac{\partial F}{\partial N}\right)_{V,T}$$

NPT: Gibbs free energy

$$\mu \equiv \left(\frac{\partial G}{\partial N}\right)_{P,T}$$

$$\beta G = -\ln\left(Q_{NPT}\right) \qquad Q_{NPT} = \frac{1}{\Lambda^{3N} N!}\int \mathrm{d}V V^N \exp\left(-\beta V P\right)\int \mathrm{d}s^N \exp\left[-\beta U\left(s^N; L\right)\right]$$

$$\beta\mu = \frac{\beta G\left(N+1\right) - \beta G\left(N\right)}{N+1-N} \qquad \beta\mu = -\ln\frac{Q\left(N+1\right)}{Q\left(N\right)}$$

$$\beta\mu = -\ln\frac{\frac{1}{\Lambda^{3N+3}\left(N+1\right)!}}{\frac{1}{\Lambda^{3N} N!}}\left(\frac{\int \mathrm{d}V V^{N+1}\exp\left(-\beta V P\right)\int \mathrm{d}s^{N+1}\exp\left[-\beta U\left(s^{N+1};L\right)\right]}{\int \mathrm{d}V V^{N}\exp\left(-\beta V P\right)\int \mathrm{d}s^{N}\exp\left[-\beta U\left(s^{N};L\right)\right]}\right)$$

$$\beta\mu = -\ln$$

The volume fluctuates!

$$\left\langle \frac{\beta P V}{N+1}\int \mathrm{d}s_{N+1}\exp\left(-\beta\Delta U^{+}\right)\right\rangle \neq \left\langle \frac{\beta P V}{N+1}\right\rangle\left\langle \int \mathrm{d}s_{N+1}\exp\left(-\beta\Delta U^{+}\right)\right\rangle$$

$$\beta\mu = \ln$$

$$\beta\mu = \ln\left(\Lambda^3\beta P\right) - \ln\left\langle \frac{\beta P V}{N+1}\int \mathrm{d}s_{N+1}\exp\left(-\beta\Delta U^{+}\right)\right\rangle$$

Widom particle insertion

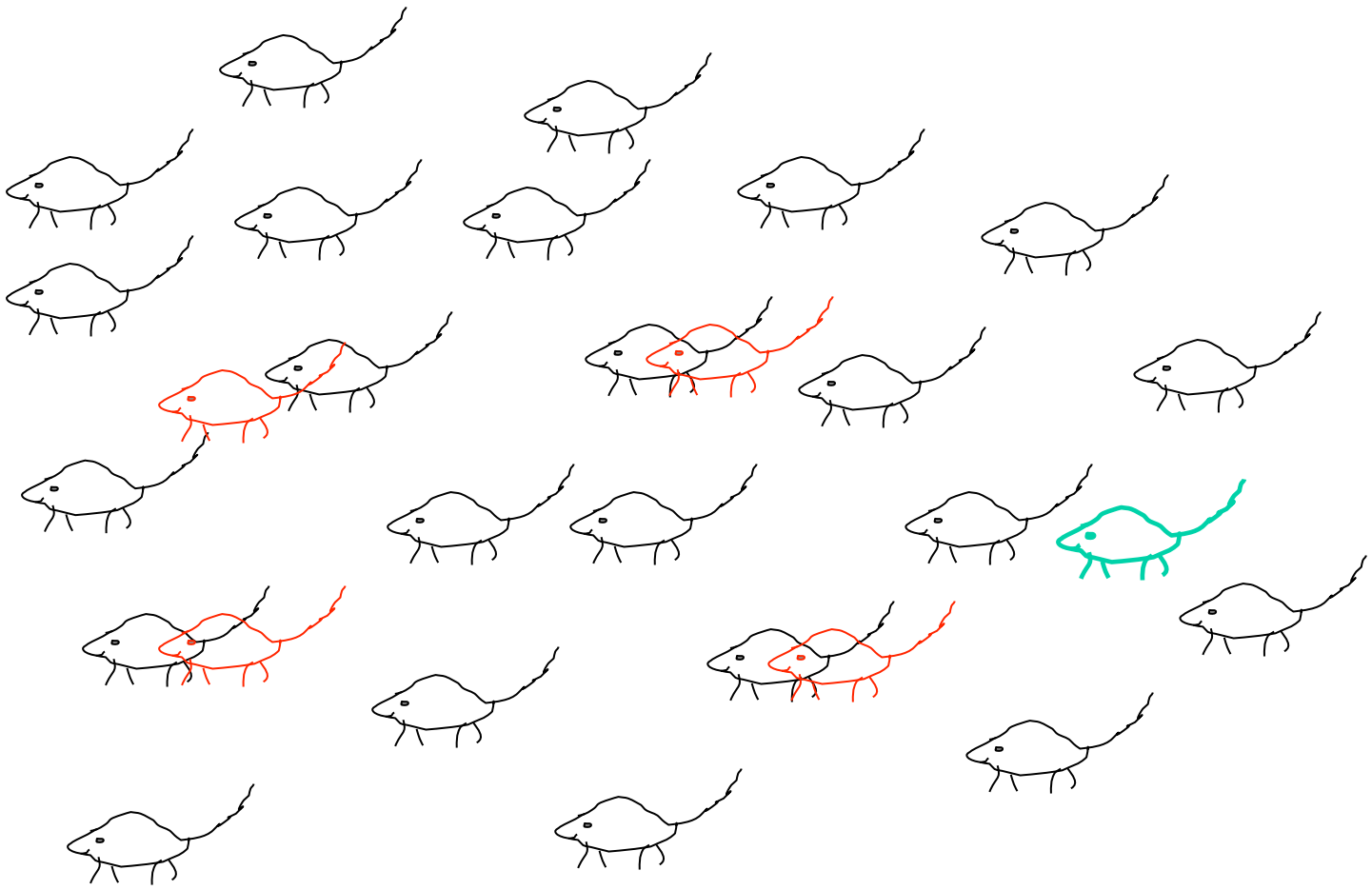
NVT:

$$\beta\mu = \beta \ln(\rho) - \ln\left\langle \int \mathrm{ds}_{N+1} \exp\left[-\beta\Delta U^{+}\right]\right\rangle_{NVT}$$

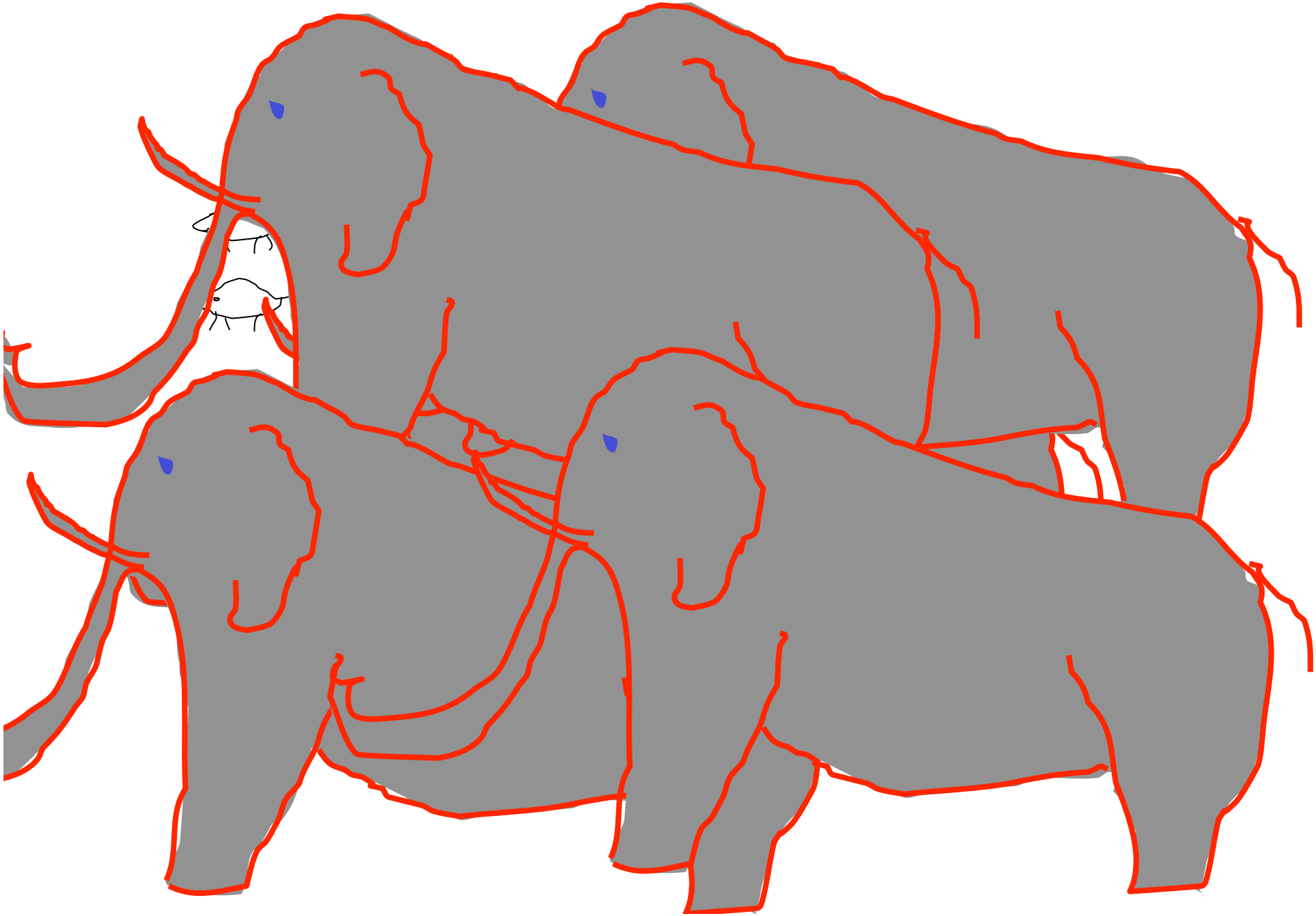
NPT:

$$\beta\mu = \ln\left(\Lambda^{3}\beta P\right) - \ln\left\langle \frac{\beta PV}{N+1} \int \mathrm{ds}_{N+1} \exp\left(-\beta\Delta U^{+}\right)\right\rangle$$

ACCEPTANCE OF RANDOM INSERTION DEPENDS ON SIZE



ACCEPTANCE OF RANDOM INSERTION DEPENDS ON SIZE



ACCEPTANCE OF RANDOM INSERTION DEPENDS ON DENSITY

Insertion easy

Insertion difficult

Particle insertion continued….

$$\mu \approx \left(\frac{F(N+1,V,T) - F(N,V,T)}{(N+1) - N} \right)$$

therefore

$$\mu \approx -kT \ln \frac{Q(N+1,V,T)}{Q(N,V,T)}$$

But also

$$\mu \approx +kT \ln \frac{Q(N,V,T)}{Q(N+1,V,T)}$$

Interpreted as particle **removal**

As before:

$$Q(N,V,T) = \frac{1}{N!\Lambda^{3N}} \int dr^N \exp(-\beta U(r^N) =$$

$$\frac{1}{N!\Lambda^{3N}} V^N \int ds^N \exp(-\beta U(s^N; L)$$

With **s** a scaled coordinate: $0 \leq \mathbf{s} < 1$

r = L **s** (is box size)

$$\frac{Q(N,V,T)}{Q(N+1,V,T)} =$$

$$\frac{(N+1)\Lambda^3}{V}\frac{\int ds^N \exp(-\beta U(s^N)}{\int ds^{N+1} \exp(-\beta U(s^{N+1})}$$

$$= \frac{(N+1)\Lambda^3}{V}\frac{\int ds_{N+1} \int ds^N \exp(-\beta U(s^N)}{\int ds^{N+1} \exp(-\beta U(s^{N+1})}$$

However, now write

$$U((s^N) \equiv U(s^{N+1}) - \Delta U(s_{N+1}, s^N)$$

$$\frac{Q(N,V,T)}{Q(N+1,V,T)} =$$

$$\frac{(N+1)\Lambda^3}{V}\langle \exp(+\beta \Delta U(s_{N+1}, s^N)\rangle_{N+1}$$

And therefore

$$\mu = \mu_{id.gas} + kT \ln\left(\langle \exp(+\beta \Delta U(s_{N+1}, s^N)\rangle_{N+1}\right)$$

Positive sign!

Interpretation:

1. Evaluate ΔU for a random **REMOVAL** of a molecule in a system containing N+1 molecule.
2. Compute $\exp(+\beta \Delta U)$
3. Repeat M times and compute the average "Boltzmann factor"
4. Then

$$\mu_{excess} = +kT \ln < \exp(+\beta \Delta U) >$$

This approach DOES NOT WORK

What is wrong?

$\exp(+\beta \Delta U)$ is not bounded. The average that we compute can be dominated by INFINITE contributions from points that are NEVER sampled.

What to do?

Consider the energy distribution upon insertion:

$$p_0(\Delta U) \equiv \frac{\int \exp(-\beta U_N)\delta(\Delta U - U_{N+1} + U_N)}{\int \exp(-\beta U_N)}$$

And also consider the energy distribution for removal

$$p_1(\Delta U) \equiv \frac{\int \exp(-\beta U_{N+1})\delta(\Delta U - U_{N+1} + U_N)}{\int \exp(-\beta U_{N+1})}$$

p_0 and p_1 are related:

$$p_1(\Delta U) = \frac{\int \exp(-\beta(U_N + \Delta U))\delta(\Delta U - U_{N+1} + U_N)}{Q_{N+1}}$$

$$= \exp(-\beta \Delta U)\frac{\int \exp(-\beta U_N)\delta(\Delta U - U_{N+1} + U_N)}{Q_{N+1}}$$

$$\ln p_1(\Delta U) = \beta(\Delta F - \Delta U) + \ln p_0(\Delta U)$$

$$f_0(\Delta U) \equiv \ln p_0(\Delta U) - 0.5\beta\Delta U$$

$$f_1(\Delta U) \equiv \ln p_1(\Delta U) + 0.5\beta\Delta U$$

$$\beta\Delta F$$

$$f_1(\Delta U) \equiv C_1$$

Fit f_0 and f_1 to two polynomials that only differ by a constant.

Simulate system 0: compute f_0

Simulate system 1: compute f_1

$$f_0(\Delta U) \equiv C_0 + a\Delta U + b\Delta U^2 + c\Delta U^3$$

$$\beta\Delta F = C_1 - C_0$$

This is known as the overlapping distribution method (sec 7.2.3)

μ from overlapping distributions

System 0: *N-1, V,T, U* + 1 ideal gas

System 1: *N, V,T, U*

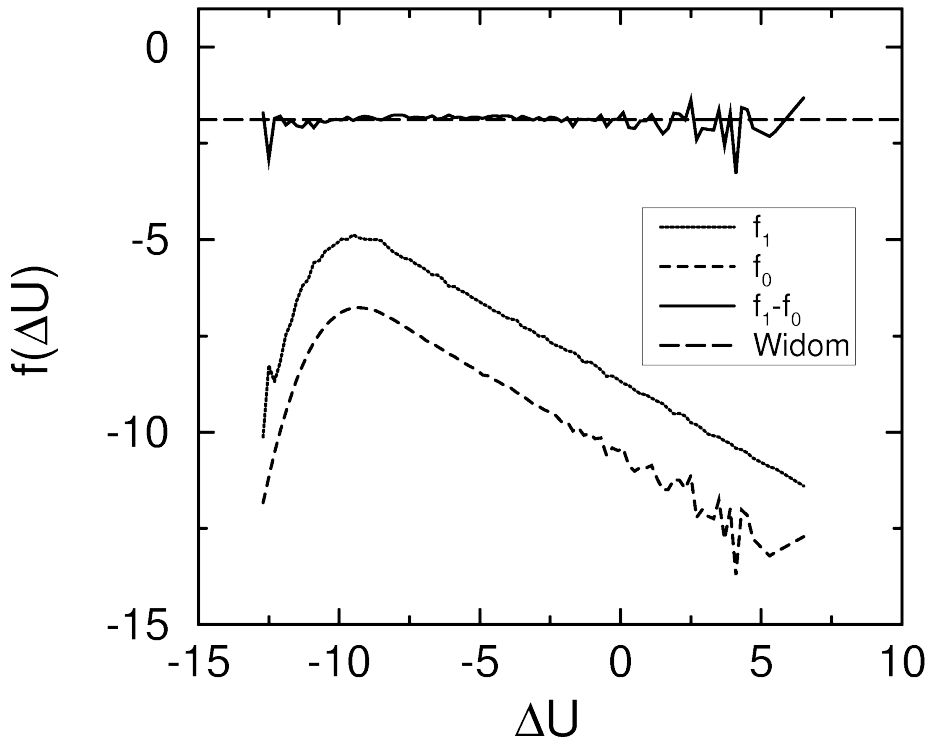
$$\Delta\beta F = \beta F_1 - \beta F_0 \equiv \beta\mu^{ex}$$

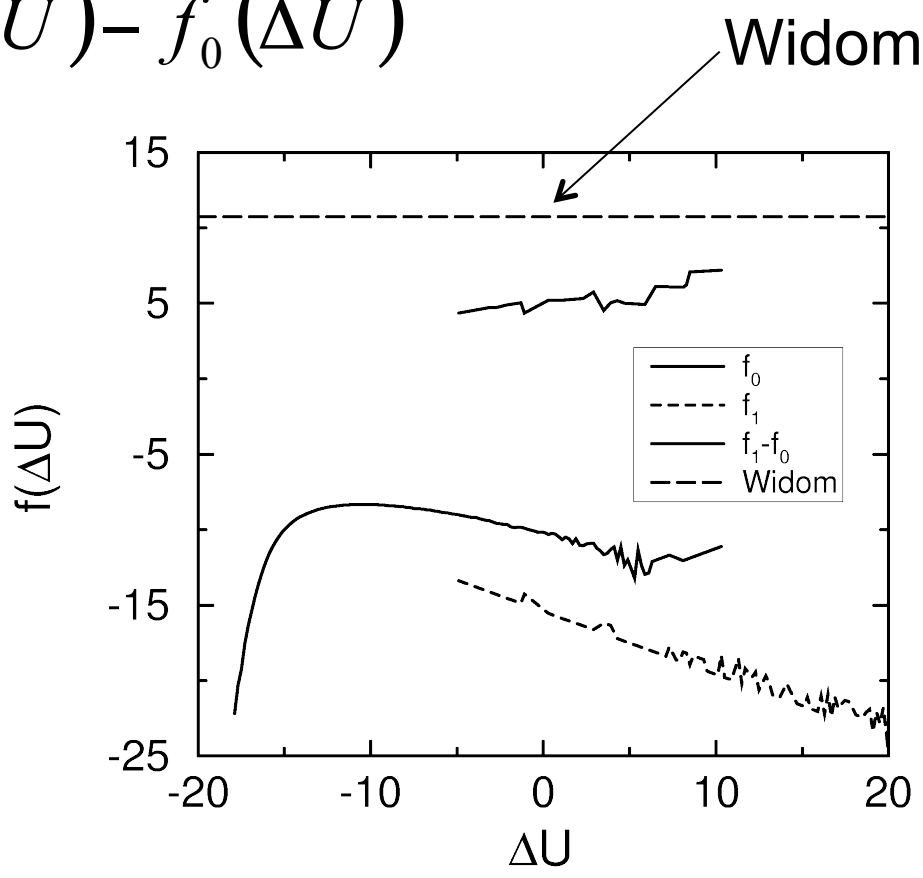
$$\Delta U = U_1 - U_0$$

System 0: test particle energy

System 1: real particle energy

$$\beta\mu^{ex} = f_1(\Delta U) - f_0(\Delta U)$$





Does it work for hard spheres?

consider ΔU=0

$$f_1(0) = f_0(0) + \beta\mu$$

$$f_1(0) = \ln(1) + (constant)$$

$$f_0(0) = \ln(P_{acc}) + (constant)$$

$$\beta\mu = -\ln(P_{acc})$$

YES!

Advanced MC Sampling

- Exotic ensembles

- Improved sampling:
  - Rejectionless cluster moves
  - include rejections: waste recycling

- Computing the chemical potential
  - Widom insertion
  - overlapping distributions

- **Biased sampling: umbrella sampling**

- The problem of computer time

From histograms to free-energy landscapes

The function $p(\Delta U)$ is an example of a histogram where $\Delta U(\mathbf{r}^N)$ plays the role of the coordinate. We can consider other coordinates $Q(r^N)$. Examples…

The probability that $Q(r^N)$ has a value Q is given by

$$P(Q_0) = \frac{\int \exp(-\beta U(r^N))\delta(Q(r^N) - Q_0)}{\int \exp(-\beta U(r^N))}$$

From this probability we can derive (`define') the variation of the free energy with Q:

$$F(Q) = -kT \ln(P(Q)) + \text{constant}$$

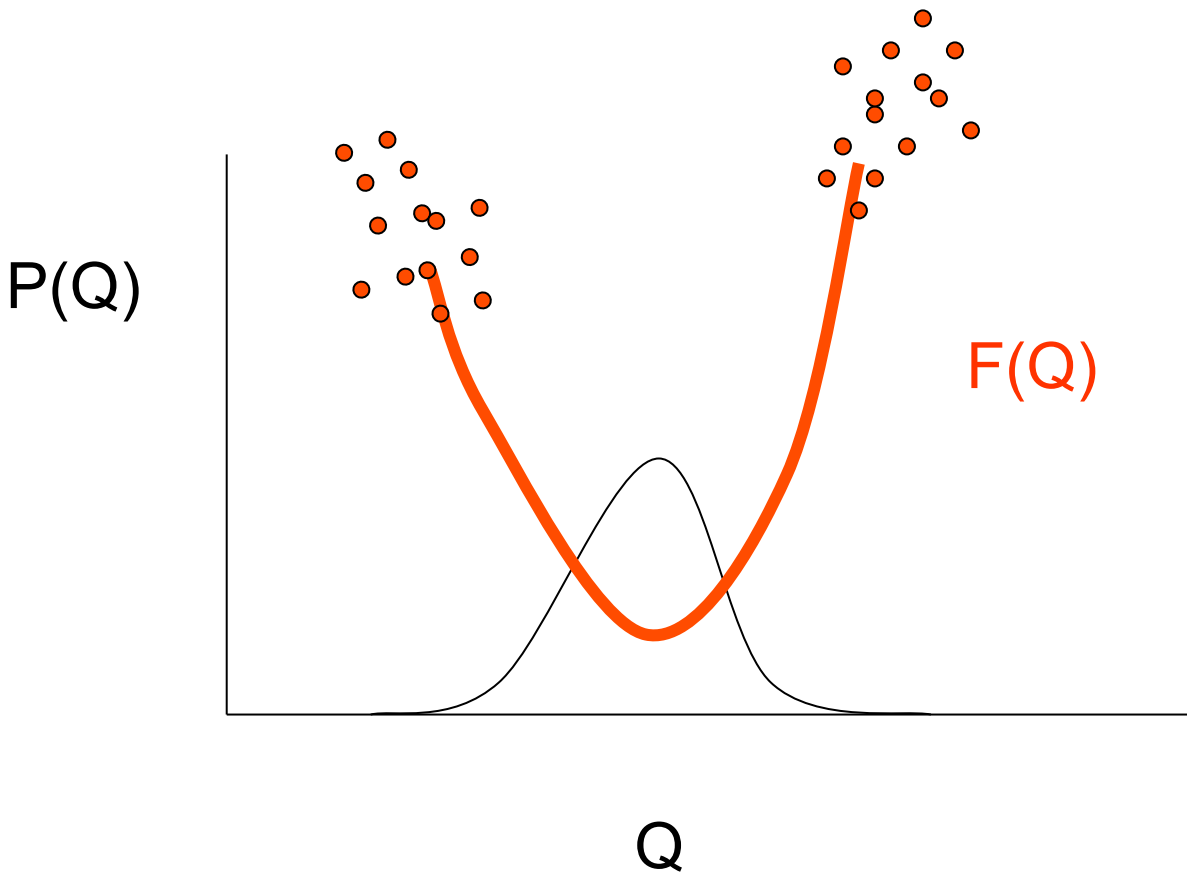
From histograms to free-energy landscapes

Free energy landscapes are interesting in many different contexts (phase transitions, protein folding, …)

Sampling a free energy landscape is easy near the minima, and difficult near the maxima because P(Q) is small where F(Q) is large..

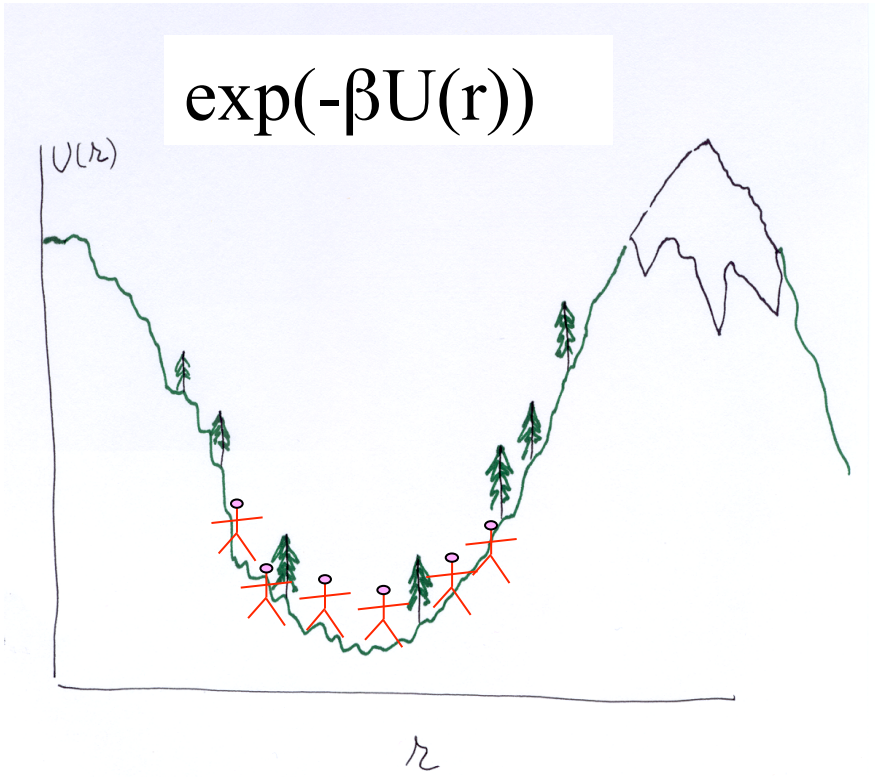
$$F(Q) = -kT \ln(P(Q)) + \text{constant}$$

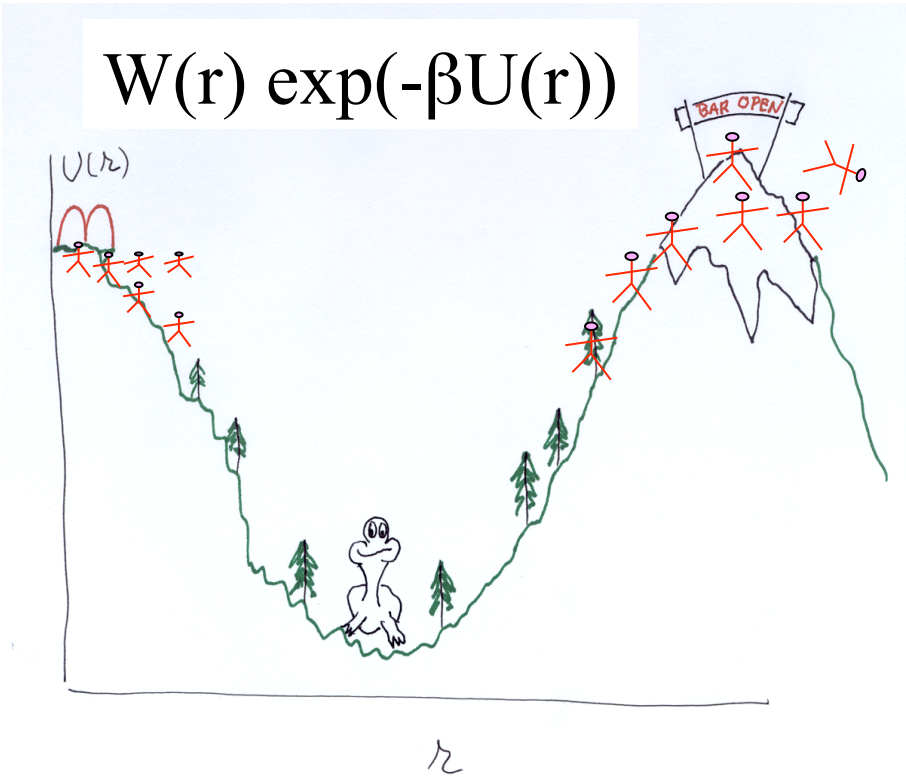
Naively, we could sample determine F(Q) by accumulating a histogram of the spontaneous fluctuations of Q.



Problem: F(Q) is very noisy, except near its minimum.

Biased sampling





METROPOLIS SAMPLING

BIASED SAMPLING

Application of biased MC simulation to determine $P_w(Q)$

$$P_w(Q_0) = \frac{\int \exp[-\beta(U(r^N) + w(Q(r^N))]\delta(Q(r^N) - Q_0)}{\int \exp[-\beta(U(r^N) + w(Q(r^N))]}$$

But this we can rewrite as

$$P_w(Q_0) = \exp(-\beta w(Q_0))\frac{\int \exp[-\beta U(r^N)]\delta(Q(r^N) - Q_0)}{\int \exp[-\beta(U(r^N) + w(Q(r^N))]}$$

Ideally, we should choose w(Q) = -F(Q), because then the biased histogram would be flat.
But, of course, we don't know F(Q) a priori…

Once we know the biased histogram

$$P_w(Q_0) = c \exp(-\beta w(Q_0)) P(Q_0)$$

we can reconstruct the unbiased histogram – up to a constant

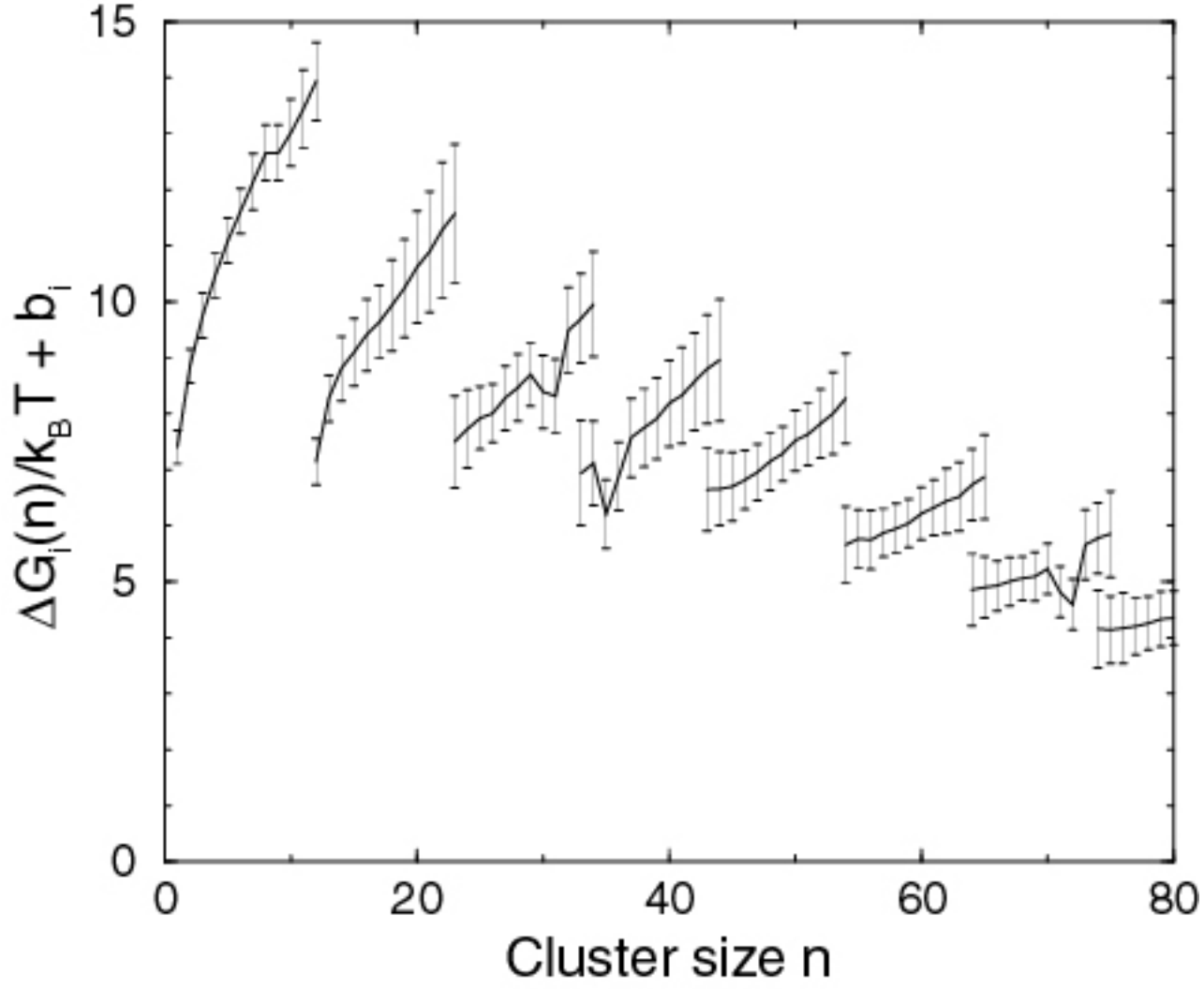
$$-kT \ln(P(Q_0)) = -kT \ln(P_w(Q_0)) + w(Q_0) - kT \ln c$$

$$F(Q_0) = -kT \ln(P_w(Q_0)) + w(Q_0) - kT \ln c$$

In summary: We can choose the bias w(Q) such that any desired range of Q-values is sampled.

And we can correct for the bias.

For obscure reasons this is often called umbrella sampling

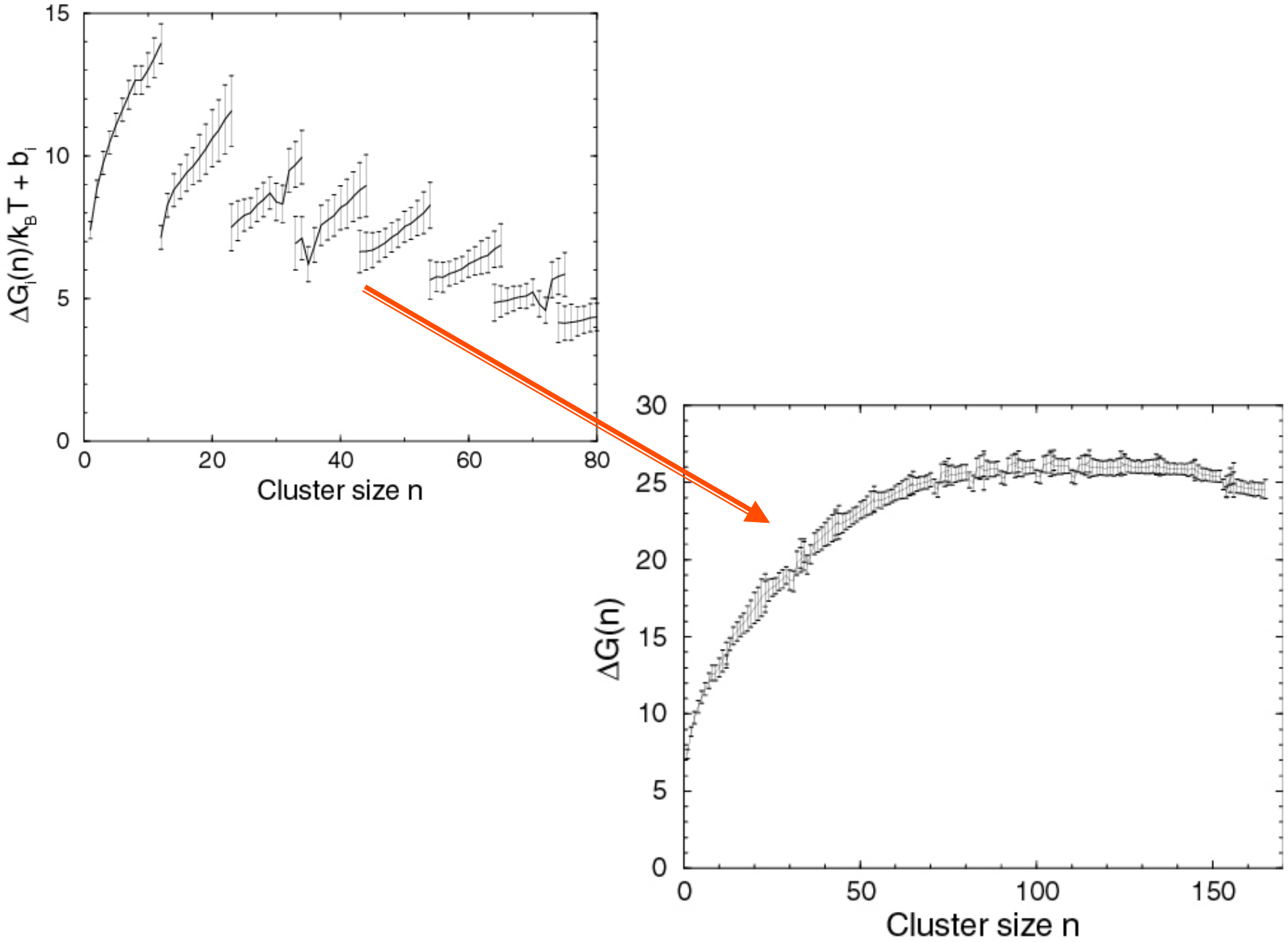


The only remaining problem is that the different parts of F(Q) are shifted with respect to each other.

Solutions:

1. Fit to a single curve (not very elegant, but effective)
2. Use `Ferrenberg-Swendsen' scheme to combine different parts of the histogram (more elegant, but more sensitive to noise)
3. Use the WHAM method of Kumar et al. or MBAR from Chodera et al.

Result:


15
10
5
0
0
20
40
60
80
$\Delta G_i(n)/k_B T + b_i$
Cluster size n
30
25
20
15
10
5
0
0
50
100
150
$\Delta G(n)$
Cluster size n

FINALLY…

There is NEVER enough computer time

Solutions:

1. Wait until there is enough computer power

Moore's law: computing power Γ increases a factor 10 every 5 years

$$\Gamma(\Delta t) = \Gamma_0 e^{\Delta t/\tau}$$

with $\tau \approx 2.17$ years.

When to start a major calculation?

Either start now, or wait a time Δt and use the computers that are available then:

For a computation involving X operations, the expected time to completion, using the current computing power Γ_0, is: $t_0 = \frac{X}{\Gamma_0}$.

But if we first wait a time Δt, it is:

$$t = \Delta t + \frac{t_0}{e^{\Delta t/\tau}}$$

Optimum? Compute extremum:

$$0 = 1 - \frac{t_0}{\tau} e^{-\Delta t/\tau}$$

Hence

$$1 = \frac{t_0}{\tau} e^{-\Delta t/\tau}$$

No solutions if $t_0 < \tau$, i.e. if the estimated computing time is less than 2.17 years.

In that case: start right away!

Otherwise:

wait for a time interval

$$\Delta t = \tau \ln(t_0/\tau)$$

then buy a computer, and start!!!

Solutions:

1. Wait until there is enough computer power
2. **Use cheaper models/ more efficient algorithms.**

The End