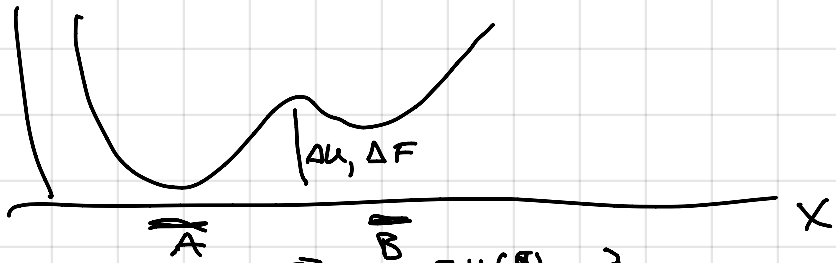
Enhanced Sampling

Suppose $U(x)$ or $F(x)$



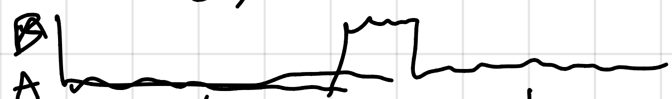
$$F(\vec{x}) = -kT\log\int \delta(M(\vec{q})-\vec{X})\, e^{-\beta u(\vec{q})}\, d\vec{q} \;-F_0$$

(Potential of mean force)

$\text{Rate}_{A\to B} \propto e^{-\beta\Delta u^{\ddagger}}$ or $e^{-\beta\Delta F^{\ddagger}}$,

So if $1/\text{rate} \gg N\Delta t$, then you will be trapped in A (or B)

(rare event problem)



We need tricks to overcome this problem!

These are called enhanced or accelerated sampling methods, and generally estimate the (free)-energy diff between A & B too

($\Delta A = -kT\log P_B/P_A$ ← like equilibrium const

Idea! increase temp → rate faster

$T \propto \langle KE \rangle$

$$\langle A\rangle_{T_1} = \int dx\, P_1(x)\, A(x)$$

$$P_1(x) = \omega_1(x)/Z_1 \,, \quad \text{eg } \frac{e^{-u(x)/k_BT_1}}{\int dx\, e^{-u(x)/k_BT_1}}$$

$$\langle A\rangle_{T_1} = \int dx\, A(x)\, \frac{\omega_1(x)}{Z_1} \cdot \frac{w_2(x)}{Z_2} \cdot \frac{w_2(x)}{Z_2}$$

$$= \int dx\, A(x)\, \frac{\omega_2(x)}{Z_2} \cdot \left(\frac{w_1(x)}{w_2(x)}\right) \cdot \frac{Z_2}{Z_1}$$

$$= \frac{Z_2}{Z_1} \cdot \int dx\, A(x)\, \frac{w_1(x)}{w_2(x)} \cdot \left[\frac{W_2(x)}{Z_2}\right]_{\sim P_2(x)}$$

$$= Z_2/Z_1 \langle A\, \omega_1/\omega_2 \rangle_{T_2}$$

for N, U, T $\quad = Z_2/Z_1 \left\langle A\, e^{-\frac{1}{k_BT_1}u(x)}\, e^{+\frac{1}{k_BT_2}u(x)} \right\rangle_{T_2}$

$$= Z_2/Z_1 \left\langle A\, e^{-\frac{u(x)}{k_B}\left(\frac{1}{T_1} - \frac{1}{T_2}\right)} \right\rangle_{T_2}$$

$$Z_1/Z_2 = \frac{\int dx\, \omega_1(x)}{Z_2} = \frac{\int dx\, w_1(x) \cdot \frac{W_2(x)}{w_2(x)}}{Z_2} = \left\langle \frac{W_1(x)}{w_2(x)} \right\rangle_{T_2}$$

Concisely:

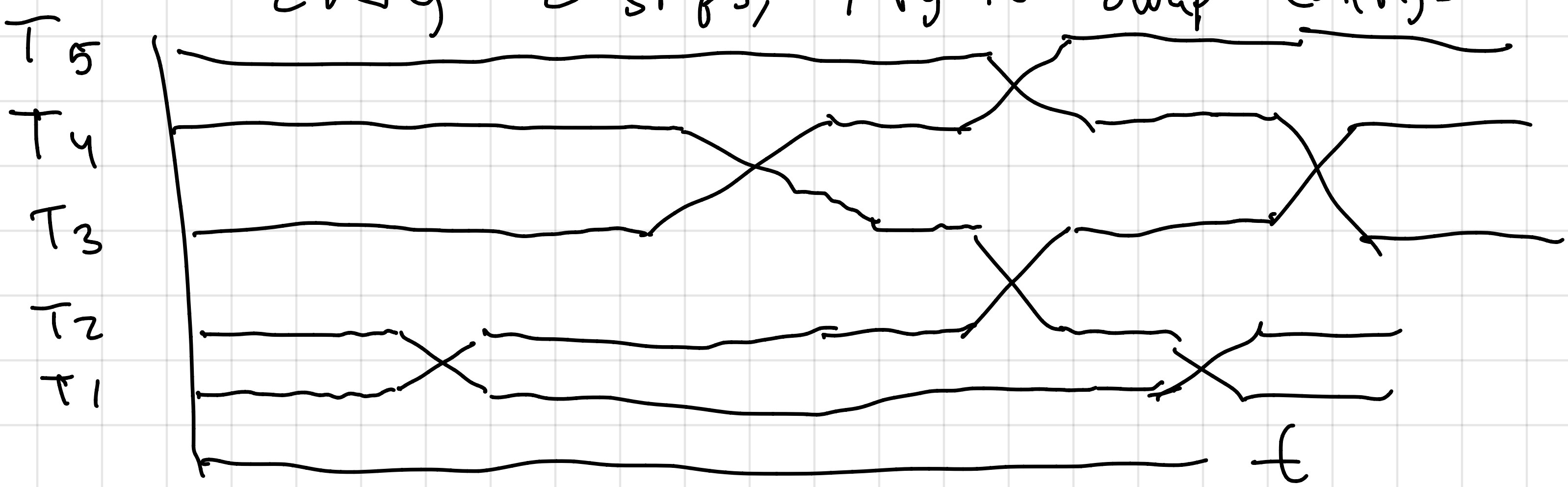
$$\langle A_{T_1}\rangle = \langle A\, \omega_1/\omega_2 \rangle_{T_2} \Big/ \langle \omega_1/\omega_2 \rangle_{T_2}$$

if $T_2 \gg T_1$, weights very small, numerical problem

Solution, run many sims @ diff T so $\frac{1}{T_i} - \frac{1}{T_{i+1}}$ not too big

Replica exchange MD / Parallel tempering [didn't talk about const T yet?

Every τ steps, try to swap configs



Then sample can be heated up & cooled down to T_1, overcoming barrier but still sampling @ T_1

Exchange prob? $P(A \to B)\, P(A) = P(B \to A)\, P(B)$

$$A = \{ \vec{x} @ T_\ell ,\ \vec{y} @ T_h \}$$

$$B = \{ \vec{x} @ T_h ,\ \vec{y} @ T_\ell \}$$

$$P(A \to B) = \min\left(1, P(B)/P(A)\right) = \min\left(1, \frac{e^{-U(x)/kT_h}\, e^{-U(y)/kT_\ell}}{e^{-U(x)/kT_\ell}\, e^{-U(y)/kT_h}}\right)$$

$$\Rightarrow P(A \to B) = \min\left(1, e^{-U(x)/k\left(\frac{1}{T_h} - \frac{1}{T_\ell}\right)} \cdot e^{-\frac{U(y)}{k}\left(\frac{1}{T_\ell} - \frac{1}{T_h}\right)}\right)$$

$$= \min\left(1, e^{-\left[\frac{U(x)-U(y)}{k} \cdot \left(\frac{1}{T_h} - \frac{1}{T_\ell}\right)\right]}\right)$$

if $T_\ell < T_h$, $\frac{1}{T_h} - \frac{1}{T_\ell} < 0$ and $U(x) - U(y)$ prob < 0

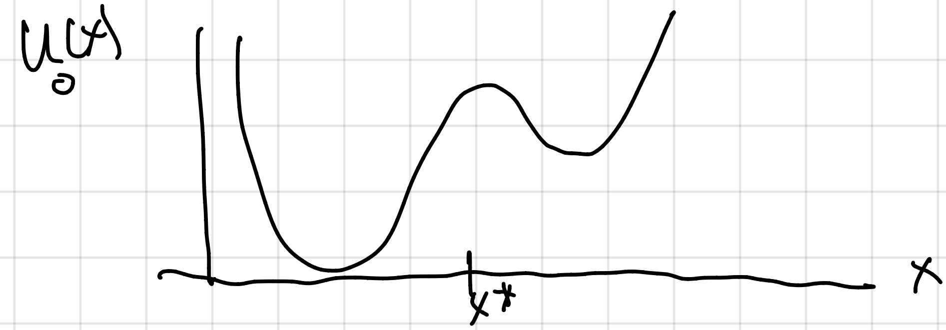
so swaps usually have prob < 1

Now since swaps satisfy detailed balance and MD or MC @ each temp satisfies detailed balance, have a chain of

$X_i @ T_1$ st $P(x_i) \to e^{-U(x_i)/k_B T_\ell}$ &

$$\langle A \rangle \sim \lim_{N \to \infty} \sum_{i=1}^{N} A(x_i^{T_1})$$

Idea #2 Go back to this picture

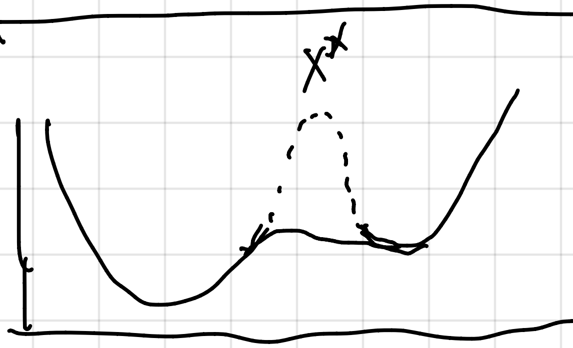


Idea: Torrie, Valleau 1977

what if we add a potential to this to reduce the barrier and correct for the effect

Example $u'(x)$

Then $U_1(x) = U_0(x) + u'(x)$



This will give fast transitions from $L \to R$

But how do we get $\langle A \rangle = \int A(x) P_0(x)$ when

we are simulating with U_1 and

hence $P_1(x) = e^{-\beta U_1(x)} / Z_1 = w_1(x)/Z_1$

We actually did this before, perturbation theory

$$\langle A \rangle_0 = \frac{1}{Z_0} \int dx\, A(x)\, e^{-\beta u_0(x)}$$

like before, mult by $e^{-\beta u_1(x)}/Z_1$ in top and

$$= \frac{1}{Z_0} \int dx\, A(x)\, e^{-\beta u_0(x)} \cdot \frac{e^{-\beta u_1(x)}}{e^{-\beta u_1(x)}} \cdot \frac{Z_1}{Z_1}$$

$$\exp(-\beta u_0(x))/\exp(-\beta u_1(x)) = \exp(-\beta u_0(x) + \beta u_1(x))$$
$$= \exp(-\beta u_0(x) + \beta(u_0(x) + u'(x)))$$

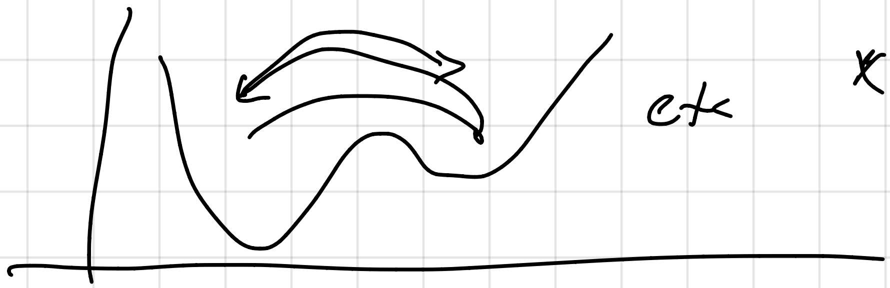
$$= Z_1/Z_0 \int dx\, A(x) e^{+\beta u'(x)} \cdot \frac{e^{-\beta u_1(x)}}{Z_1}$$

$$= \langle A e^{+\beta u'(x)} \rangle_1 / \langle e^{+\beta u'(x)} \rangle_1 = \frac{\langle A/w \rangle_1}{\langle 1/w \rangle_1}$$

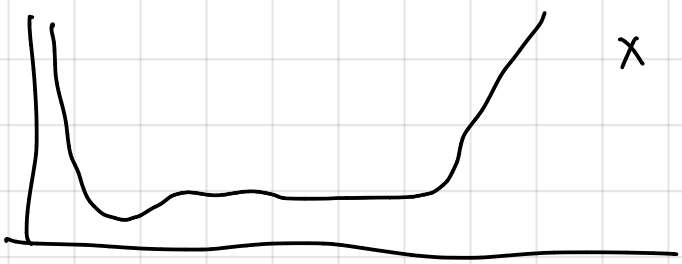
what is this weight doing? correcting for every time there is something near X^* it should have less weight

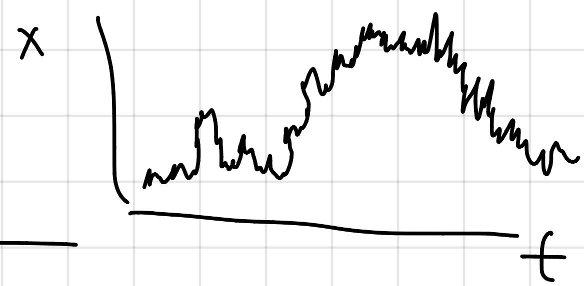
This works well for a simple 1d barrier crossing, but it does not necessarily make the simulation averages converge very fast.

I said for the average to be computed well, you should see every state multiple times



with perturb





now, diffusion

Diffusion $\langle \delta x^2 \rangle \propto Dt$

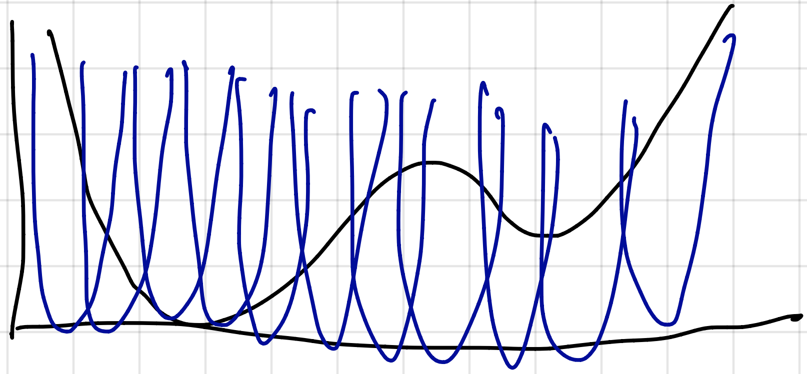
so to explore whole space, $t \sim L^2/D$

if D is small or space is big will take a long time

Later idea: Umbrella Sampling (umbrella, cover all the space)

Many biased simulations with different ω' to make sure all space is covered

So Eg:



Common to use $U_i'(x) = \frac{1}{2}k\,[x - x_i]^2$

if instead $U_i'(x) = \begin{cases} 0 & |x - x_i| < a \\ \infty & \end{cases}$ boxes

Potential $U_i(x) = U_0(x) + U_i'(x)$

$= U_0(x)$ inside box

Now if $U(x)$ is actually PMF we don't know, to get that we need to compute

$$A_i = -k_BT \log\left[\int dx\, \chi_i(x)\, e^{-\beta U_0(x)} \Big/ \int dx\, e^{-\beta U_0(x)}\right]$$

where $\chi = \begin{cases} 1 & |x - x_i| < a \\ 0 & \text{otherwise} \end{cases}$

can do this with

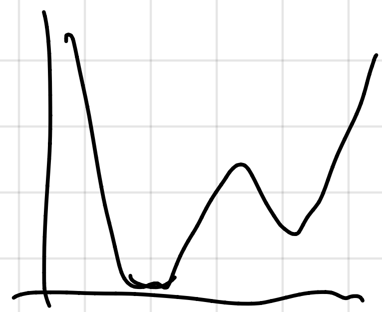
$$\langle \chi(x)/w_i'(x) \rangle_i / \langle 1/w_i'(x) \rangle_i$$

will get something like

etc

don't know offsets but must be equal at boundaries

$\rightarrow$ $\log P(x)$



Methods exist to combine samples with other biasing functions

Next: Use this for phase transitions