Enhanced Sampling

Suppose \( U(x) \) or \( F(A) \)

\[ F(A) = -KT \log S(M(x) - 1) e^{-\beta u(x) d^2} - F_0 \]

(Potential of mean force)

Rate \( A \rightarrow B \) \( \propto e^{-PA^+} \) or \( e^{-PA^+} \)

So if \( \text{rate} \gg N \Delta t \), 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 difference between \( A \) and \( B \):

\[ \Delta A = -kT \log \frac{P_{B}}{P_{A}} \]

\( \Delta A \) like equilibrium constant

Idea: increase temp \( \rightarrow \) rate faster

\[ T \propto \langle ke^\gamma \rangle \]

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\[ <A>_{T_1} = \int dx \, P_1(x) \, A(x) \]

\[ P_1(x) = \frac{\omega_1(x)}{Z_1} \]

\[ e^{-\mu(x) / k_B T_1} \]

\[ <A>_{T_1} = \int dx \, A(x) \, \frac{\omega_1(x)}{Z_1} \cdot \frac{\omega_2(x)}{Z_2} = \frac{Z_2}{Z_1} \cdot \int dx \, A(x) \, \frac{\omega_1(x)}{\omega_2(x)} \cdot \frac{\omega_2(x)}{Z_2} = \frac{Z_2}{Z_1} \cdot \int dx \, A(x) \, \frac{\omega_1(x)}{\omega_2(x)} = \frac{Z_2}{Z_1} \cdot \langle A \frac{\omega_1}{\omega_2} \rangle_{T_2} \]

For \( N, U, T = \frac{Z_2}{Z_1} \cdot \langle A e^{-\frac{1}{k_B T_1} \mu_1(x) + \frac{1}{k_B T_2} \mu_2(x)} \rangle_{T_2} \)

\[ = \frac{Z_2}{Z_1} \cdot \langle A e^{-\frac{1}{k_B T_1} \mu_1(x)} e^{\frac{1}{k_B T_2} \mu_2(x)} \rangle_{T_2} \]

\[ \frac{Z_1}{Z_2} = \int dx \, \omega_1(x) = \int dx \, \omega_1(x) \cdot \frac{\omega_2(x)}{\omega_2(x)} = \langle \frac{\omega_1(x)}{\omega_2(x)} \rangle_{T_2} \]

Concisely:

\[ <A_{T_1}^{-1} > = \frac{< A \frac{\omega_1}{\omega_2} >_{T_2}}{< \frac{\omega_1}{\omega_2} >_{T_2}} \]
If $T_2 \gg T_1$, weights very small, numerical problem

Solution, run many sims @ drift $T_2$

$1/T_i \approx 1/T_{i+1}$ not too big

Replica exchange MD / Parallel Tempering

Every 2 steps, try to swap configs

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

Exchange prob? $P(CA \Rightarrow B) P(CA) = P(B \Rightarrow A) P(CB)$

$A = \{ \exists x \in T_e, y \in T_h \}$

$B = \{ \exists x \in T_h, y \in T_e \}$
\[ P(A \rightarrow B) = \min \left( 1, \frac{P(B)}{P(A)} \right) = \min \left( 1, \frac{e^{-\frac{u(x)}{kT}}}{e^{-\frac{u(y)}{kT}}} \right) \]

\[ \Rightarrow P(A \rightarrow B) = \min \left( 1, e^{-\frac{u(x)}{k} \left( \frac{1}{T_1} - \frac{1}{T_2} \right) - \frac{u(y)}{k} \left( \frac{1}{T_1} - \frac{1}{T_2} \right)} \right) \]

\[ = \min \left( 1, e^{-\frac{u(x) - u(y)}{k} \left( \frac{1}{T_1} - \frac{1}{T_2} \right)} \right) \]

If \( T_1 < T_2 \), \( \frac{1}{T_1} - \frac{1}{T_2} < 0 \) 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

\[ x_i \in T_1 \text{ s.t. } P(x_i) \rightarrow e^{-\frac{\Delta E}{kT}} \text{, } \& \]

\[ \langle A \rangle \sim \lim_{N \to \infty} \frac{1}{N} \sum_{i=1}^{N} A(x_i) \]
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 $u(x) = u_0(x) + u'(x)$

This will give fast transitions from L to R

But how do we get

$\langle A \rangle = \int A(x) P_0(x) \, dx$ when

we are simulating with $u_0$ and

hence

$P_0(x) = \frac{e^{-\beta u_0(x)/2}}{Z_1} = \frac{\omega_0(x)}{Z_1}$,
We actually did this before, perturbation theory:

\[ \langle A \rangle_0 = \int_{-\infty}^{\infty} \frac{dx}{Z_0} A(x) e^{-\beta U_0(x)} \]

like before, mult by \( \frac{e^{-\beta U(x)}}{Z_1} \) in top and

\[ = \int_{-\infty}^{\infty} \frac{dx}{Z_0} A(x) e^{Bu(x)} \cdot \frac{e^{-\beta U(x)}}{e^{-\beta U(x)} - 1} \]

\[ = \frac{Z_1}{Z_0} \int_{-\infty}^{\infty} dx \frac{A(x) e^{Bu(x)}}{e^{-\beta U(x)} - 1} \]

\[ = \exp(-\beta U_0(x)) / \exp(-\beta U(x)) = \exp(-\beta U_0(x) + Bu(x)) \]

\[ = \exp(-\beta U_0(x) + pU_0(x) + U(x)) \]

\[ = \frac{ZA/W^2}{\langle e^{Bu(x)} \rangle_1} = \frac{CA/W^2}{\langle 1/w \rangle_1} \]

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.

Now, diffusion:

\[ \langle S^2 \rangle \propto D t \]

so to explore whole space, \( t \sim \frac{L^2}{D} \)

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 \( w \) to make sure all space is covered.
Common to use $U_i'(x) = \frac{1}{2} \kappa (x - y_i)^2$

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

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 how to get that we need to compute

$A_i = -13.3 T \log \left[ \int dx \chi(x) e^{-\mu_0 \alpha x} / \int dx e^{-\beta \phi(x)} \right]$

Where $\chi = \begin{cases} 1 & |x - x_i| < a \\ 0 & o.w. \end{cases}$

can do this with

$\langle \chi(x)/w_i'(x) \rangle / \langle 1/w_i'(x) \rangle$. 
will get something like

\[ P(x) \]

\[ \Rightarrow \log P(x) \]

Methods exist to combine samples with other biasing functions.

Next: Use this for phase transitions.