Using stochastic approximation and self-adjusted mixture sampling for molecular design: Some collected notes

Patrick B. Grinaway,[1,*] Julie M. Behr,[1,†] Zhiqiang Tan,[2,‡] and John D. Chodera[1,§]

[1]*Computational and Systems Biology Program, Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, New York, NY 10065*

[2]*Department of Statistics, Rutgers University, Piscataway, NJ 08854*

(Dated: December 25, 2016)

We collect some notes on using stochastic approximation with multiple self-adjusted mixture sampling simulations for molecular design problems.

Keywords: stochastic approximation; molecular simulation; computer aided ligand design; expanded ensemble; self-adjusted mixture sampling

MAXIMIZING LIGAND BINDING AFFINITY FOR A PROTEIN

Suppose we are trying to design a ligand that maximizes the binding affinity to a target protein. Let the index $j \in \{1, \ldots, m\}$ denote the ligand identity.

We define two systems with associated probability densities:

Suppose we have a protein:ligand:solvent system with probability density

$$p_{1j}(x) = e^{\zeta^*_{1j}} q_{1j}(x) \ , \ j = 1, \ldots, m \tag{1}$$

where we note the dimensionality of x may depend on the index j.

We also have a ligand:solvent system with probability density

$$p_{2j}(x) = e^{\zeta^*_{2j}} q_{2j}(x) \ j = 1, \ldots, m \tag{2}$$

Consider the expanded ensembles

$$(j, x)_1 \sim Q_1(\zeta_1, \zeta_2) \equiv \pi_{1j}(\zeta_1, \zeta_2) e^{-\zeta_{1j}} q_{1j}(x) \tag{3}$$

$$(j, x)_2 \sim Q_2(\zeta_1, \zeta_2) \equiv \pi_{2j}(\zeta_1, \zeta_2) e^{-\zeta_{2j}} q_{2j}(x) \tag{4}$$

To identify ligands with high binding affinity for a protein, we propose to design a chain with the limiting marginal distribution proportional to the binding affinity

$$p_{1j}, \ p_{2j} \propto K_j \equiv e^{\zeta^*_{2j} - \zeta^*_{1j}} \tag{5}$$

To do this, we allow the π to depend on $\zeta_1 \equiv \{\zeta_{11}, \ldots, \zeta_{1m}\}$ and $\zeta_2 \equiv \{\zeta_{21}, \ldots, \zeta_{2m}\}$ such that

$$\pi_{1j} = \pi_{2j} \equiv \pi_j(\zeta_1, \zeta_2) \tag{6}$$

Specifically, we propose

$$\pi_{1j} \pi_{2j} \equiv e^{\zeta_{2j} - \zeta_{1j}} = \frac{e^{\zeta_{2j} - \zeta_{1j}}}{\sum_{k=1}^{m} e^{\zeta_{2k} - \zeta_{1k}}} \tag{7}$$

THE ALGORITHM

The algorithm is as follows: At iteration n,

- Sample from the expanded ensemble defined by Q_1 and Q_2 for the current $(\zeta_1^{(n-1)}, \zeta_2^{(n-1)})$.

$$(l, x)_1 \sim Q_1(\zeta_1^{(n-1)}, \zeta_2^{(n-1)}) \tag{8}$$

$$(l, x)_2 \sim Q_2(\zeta_1^{(n-1)}, \zeta_2^{(n-1)}) \tag{9}$$

- Update estimates of $(\zeta_1^{(n-1)}, \zeta_2^{(n-1)})$.

$$\zeta_{1j}^{(n)} = \zeta_{1j}^{(n-1)} + n^{-1} \frac{\delta_j(l_1)}{\pi_j(\zeta_1^{(n-1)}, \zeta_2^{(n-1)})} \tag{10}$$

$$\zeta_{2j}^{(n)} = \zeta_{2j}^{(n-1)} + n^{-1} \frac{\delta_j(l_2)}{\pi_j(\zeta_1^{(n-1)}, \zeta_2^{(n-1)})} \tag{11}$$

Set $\zeta_{11}^{(n)} = \zeta_{21}^{(n)} = 0$.

NOTE: It may simplify things to break out the update of $\pi_j^{(n)}$ into an explicit recursion step instead of explicitly writing $\pi_j(\zeta_1, \zeta_2)$.

NOTE: It would be best if we can abandon using π_j and instead work in log space as $g_j \equiv -\log \pi_j$ instead, since any implementation involving π_j directly will run into numerical underflow/overflow issues otherwise.

See a simple example of this algorithm in action for a set of Gaussian distributions at this link.

ANOTHER POSSIBILITY

Set $\pi_{1j}(\zeta_1, \zeta_2) \propto e^{\zeta_{2j} - \zeta_{1j}}$ but $\pi_{2j}(\zeta_1, \zeta_2) \propto 1$.

With this choice, we have

$$(j, x)_1 \sim Q_1(\zeta_1, \zeta_2) \equiv e^{-\zeta_{2j}} q_{1j}(x) \tag{12}$$

$$(j, x)_2 \sim Q_2(\zeta_1, \zeta_2) \equiv e^{-\zeta_{2j}} q_{2j}(x) \tag{13}$$

The corresponding algorithm is as follows: At iteration n,

* patrick.grinaway@choderalab.org
† julie.behr@choderalab.org
‡ ztan@stat.rutgers.edu
§ Corresponding author; john.chodera@choderalab.org

- Sample $(l,x)_2$ from the expanded ensemble defined by Q_2 for the current $\zeta_2^{(n-1)}$.

$$(l,x)_2 \sim Q_2(\zeta_1,\zeta_2) \equiv e^{-\zeta_{2j}} q_{2j}(x) \tag{14}$$

- Update estimate of $\zeta_2^{(n-1)}$.

$$\zeta_{2j}^{(n)} = \zeta_{2j}^{(n-1)} + n^{-1}\frac{\delta_j(l_2)}{m^{-1}} \tag{15}$$

  Set $\zeta_{21}^{(n)} = 0$.

- Sample $(l,x)_1$ from the expanded ensemble defined by Q_1 for the current $\zeta_2^{(n)}$.

$$(l,x)_1 \sim Q_1(\zeta_1,\zeta_2) \equiv e^{-\zeta_{2j}} q_{1j}(x) \tag{16}$$

GENERALIZATION OF THE DESIGN PROBLEM

More generally, consider we have s different probability densities

$$p_{ij}(x) = e^{\zeta^*_{ij}} q_{ij}(x) \;\;,\;\; i = 1,\ldots,s \;\;,\;\; j = 1,\ldots,m \tag{17}$$

and we desire to design a chain where the marginal distributions of all s chains are

$$p_{ij} \propto \prod_{i'=1}^{s} e^{-\theta_s \zeta^*_{i'j}} = \exp\left[-\sum_{i'=1}^{s} \theta_s \zeta^*_{i'j}\right] \forall i = 1,\ldots,s \tag{18}$$

where the *design vector* $\Theta \equiv \{\theta_1,\ldots,\theta_s\}$ specifies how different targets and antitargets are used in weighting the design constraints.

We postulate that we can do this by defining $\pi_i(Z)$ for $Z \equiv \{\zeta_1,\ldots,\zeta_s\}$ as

$$p_{ij}(Z|\Theta) \propto \exp\left[-\sum_{i'=1}^{s} \theta_s \zeta_{i'j}\right] \tag{19}$$

THE SAMPLING SCHEME

Suppose we are proposing a transition from a molecule $\mathcal{M}_{\rm old}$ to $\mathcal{M}_{\rm new}$, where the initial molecule has configuration $x \equiv (x_{\rm core}, x_{\rm old})$ and the new molecule has configuration $x' \equiv (x'_{\rm core}, x'_{\rm new})$:

$$\mathcal{T} \;:\; (x_{\rm core}, x_{\rm old}, \mathcal{M}_{\rm old}) \to (x'_{\rm core}, x'_{\rm new}, \mathcal{M}_{\rm new}) \tag{20}$$

[JDC: We still need to incorporate the stochastic nature in the order of atom and torsion proposals into the ϕ terms.]

Hybrid scheme

Starting from $(x_{\rm core}, x_{\rm old}, \mathcal{M}_{\rm old})$, the proposal scheme is:

1. $\mathcal{M}_{\rm new} \sim P(\mathcal{M}_{\rm new}|\mathcal{M}_{\rm old})$
2. $x_{\rm new} \sim \phi(x_{\rm new}|x_{\rm core}, \mathcal{M}_{\rm old}, \mathcal{M}_{\rm new})$
3. $(x'_{\rm new}, x'_{\rm old}, x'_{\rm core}) \sim \Phi(x \to x'|\mathcal{M}_{\rm old} \to \mathcal{M}_{\rm new})$
4. Accept $(x'_{\rm core}, x'_{\rm new}, \mathcal{M}_{\rm new})$ with probability $\min\{1, \mathcal{A}[\mathcal{T}]\}$.

We impose super-detailed balance:

$$\pi(x_{\rm core}, x_{\rm old}, \mathcal{M}_{\rm old})\mathcal{P}[\mathcal{T}]\mathcal{A}[\mathcal{T}] = \pi(x'_{\rm core}, x'_{\rm new}, \mathcal{M}_{\rm new})\mathcal{P}[\tilde{\mathcal{T}}]\mathcal{A}[\tilde{\mathcal{T}}] \tag{21}$$

$$\begin{aligned}&\pi(x_{\rm core}, x_{\rm old}, \mathcal{M}_{\rm old})\, P(\mathcal{M}_{\rm new}|\mathcal{M}_{\rm old})\, \phi(x_{\rm new}|x_{\rm core}, \mathcal{M}_{\rm old}, \mathcal{M}_{\rm new})\, \Phi(x \to x'|\mathcal{M}_{\rm old} \to \mathcal{M}_{\rm new})\, \mathcal{A}[\mathcal{T}] \\ &= \pi(x'_{\rm core}, x'_{\rm new}, \mathcal{M}_{\rm new})\, P(\mathcal{M}_{\rm old}|\mathcal{M}_{\rm new})\, \phi(x'_{\rm old}|x'_{\rm core}, \mathcal{M}_{\rm new}, \mathcal{M}_{\rm old})\, \Phi(x' \to x|\mathcal{M}_{\rm new} \to \mathcal{M}_{\rm old})\, \mathcal{A}[\tilde{\mathcal{T}}]\end{aligned} \tag{22}$$

Collecting terms to compute the acceptance criteria:

$$\frac{\mathcal{A}[\mathcal{T}]}{\mathcal{A}[\tilde{\mathcal{T}}]} = \frac{\pi(x'_{\rm core}, x'_{\rm new}, \mathcal{M}_{\rm new})}{\pi(x_{\rm core}, x_{\rm old}, \mathcal{M}_{\rm old})} \frac{P(\mathcal{M}_{\rm old}|\mathcal{M}_{\rm new})}{P(\mathcal{M}_{\rm new}|\mathcal{M}_{\rm old})} \frac{\phi(x'_{\rm old}|x'_{\rm core}, \mathcal{M}_{\rm new}, \mathcal{M}_{\rm old})}{\phi(x_{\rm new}|x_{\rm core}, \mathcal{M}_{\rm old}, \mathcal{M}_{\rm new})} \frac{\Phi(x' \to x|\mathcal{M}_{\rm new} \to \mathcal{M}_{\rm old})}{\Phi(x \to x'|\mathcal{M}_{\rm old} \to \mathcal{M}_{\rm new})} \tag{23}$$

$$= \frac{e^{-u(x'_{\rm core}, x'_{\rm new}, \mathcal{M}_{\rm new}) + g(\mathcal{M}_{\rm new})}}{e^{-u(x_{\rm core}, x_{\rm old}, \mathcal{M}_{\rm old}) + g(\mathcal{M}_{\rm old})}} \frac{P(\mathcal{M}_{\rm old}|\mathcal{M}_{\rm new})}{P(\mathcal{M}_{\rm new}|\mathcal{M}_{\rm old})} \frac{\phi(x'_{\rm old}|x'_{\rm core}, \mathcal{M}_{\rm new}, \mathcal{M}_{\rm old})}{\phi(x_{\rm new}|x_{\rm core}, \mathcal{M}_{\rm old}, \mathcal{M}_{\rm new})} e^{-\Delta S[x \to x'|\mathcal{M}_{\rm old} \to \mathcal{M}_{\rm new}]} \tag{24}$$

$$= \frac{e^{-u(x'_{\rm core}, x'_{\rm new}, \mathcal{M}_{\rm new}) + g(\mathcal{M}_{\rm new})}}{e^{-u(x_{\rm core}, x_{\rm old}, \mathcal{M}_{\rm old}) + g(\mathcal{M}_{\rm old})}} \frac{P(\mathcal{M}_{\rm old}|\mathcal{M}_{\rm new})}{P(\mathcal{M}_{\rm new}|\mathcal{M}_{\rm old})} \frac{\phi(x'_{\rm old}|x'_{\rm core}, \mathcal{M}_{\rm new}, \mathcal{M}_{\rm old})}{\phi(x_{\rm new}|x_{\rm core}, \mathcal{M}_{\rm old}, \mathcal{M}_{\rm new})} e^{-w[x \to x'|\lambda=0 \to 1]} \frac{e^{-u(x,\lambda=0)}}{e^{-u(x',\lambda=1)}} \tag{25}$$

Two-stage scheme

Starting from $(x_{\rm core}, x_{\rm old}, \mathcal{M}_{\rm old})$, the proposal scheme is:

1. $\mathcal{M}_{\rm new} \sim P(\mathcal{M}_{\rm new}|\mathcal{M}_{\rm old})$
2. $(x'_{\rm old}, x'_{\rm core}) \sim \Phi_{\rm delete}(x \to x'|\mathcal{M}_{\rm old})$

3. $x'_{\text{new}} \sim \phi(x'_{\text{new}}|x'_{\text{core}}, \mathcal{M}_{\text{old}}, \mathcal{M}_{\text{new}})$
4. $(x''_{\text{new}}, x''_{\text{core}}) \sim \Phi_{\text{insert}}(x' \to x''|\mathcal{M}_{\text{new}})$
5. Accept $(x''_{\text{core}}, x'_{\text{new}}, \mathcal{M}_{\text{new}})$ with probability $\min\{1, \mathcal{A}[\mathcal{T}]\}$.

We impose super-detailed balance:

$$\pi(x_{\text{core}}, x_{\text{old}}, \mathcal{M}_{\text{old}})\mathcal{P}[\mathcal{T}]\mathcal{A}[\mathcal{T}] = \pi(x''_{\text{core}}, x''_{\text{new}}, \mathcal{M}_{\text{new}})\mathcal{P}[\tilde{\mathcal{T}}]\mathcal{A}[\tilde{\mathcal{T}}] \tag{26}$$

$$\begin{aligned}&\pi(x_{\text{core}}, x_{\text{old}}, \mathcal{M}_{\text{old}})\, P(\mathcal{M}_{\text{new}}|\mathcal{M}_{\text{old}})\, \Phi_{\text{delete}}(x \to x'|\mathcal{M}_{\text{old}})\, \phi(x'_{\text{new}}|x'_{\text{core}}, \mathcal{M}_{\text{old}}, \mathcal{M}_{\text{new}})\, \Phi_{\text{insert}}(x' \to x''|\mathcal{M}_{\text{new}})\, \mathcal{A}[\mathcal{T}] \\ &= \pi(x''_{\text{core}}, x''_{\text{new}}, \mathcal{M}_{\text{new}})\, P(\mathcal{M}_{\text{old}}|\mathcal{M}_{\text{new}})\Phi_{\text{delete}}(x'' \to x'|\mathcal{M}_{\text{new}})\, \phi(x'_{\text{old}}|x'_{\text{core}}, \mathcal{M}_{\text{new}}, \mathcal{M}_{\text{old}})\, \Phi_{\text{insert}}(x' \to x|\mathcal{M}_{\text{old}})\, \mathcal{A}[\tilde{\mathcal{T}}]\end{aligned} \tag{27}$$

Collecting terms to compute the acceptance criteria:

$$\begin{aligned}&\frac{\mathcal{A}[\mathcal{T}]}{\mathcal{A}[\tilde{\mathcal{T}}]} \\ &= \frac{\pi(x''_{\text{core}}, x''_{\text{new}}, \mathcal{M}_{\text{new}})}{\pi(x_{\text{core}}, x_{\text{old}}, \mathcal{M}_{\text{old}})} \frac{P(\mathcal{M}_{\text{old}}|\mathcal{M}_{\text{new}})}{P(\mathcal{M}_{\text{new}}|\mathcal{M}_{\text{old}})} \frac{\Phi_{\text{delete}}(x'' \to x'|\mathcal{M}_{\text{new}})}{\Phi_{\text{insert}}(x' \to x''|\mathcal{M}_{\text{new}})} \frac{\phi(x'_{\text{old}}|x'_{\text{core}}, \mathcal{M}_{\text{new}}, \mathcal{M}_{\text{old}})}{\phi(x'_{\text{new}}|x'_{\text{core}}, \mathcal{M}_{\text{old}}, \mathcal{M}_{\text{new}})} \frac{\Phi_{\text{insert}}(x' \to x|\mathcal{M}_{\text{old}})}{\Phi_{\text{delete}}(x \to x'|\mathcal{M}_{\text{old}})} && (28) \\ &= \frac{e^{-u(x''_{\text{core}}, x''_{\text{new}}, \mathcal{M}_{\text{new}}) + g(\mathcal{M}_{\text{new}})}}{e^{-u(x_{\text{core}}, x_{\text{old}}, \mathcal{M}_{\text{old}}) + g(\mathcal{M}_{\text{old}})}} \frac{P(\mathcal{M}_{\text{old}}|\mathcal{M}_{\text{new}})}{P(\mathcal{M}_{\text{new}}|\mathcal{M}_{\text{old}})} e^{-\Delta S_{\text{insert}}[x' \to x''|\mathcal{M}_{\text{new}}]} \frac{\phi(x'_{\text{old}}|x'_{\text{core}}, \mathcal{M}_{\text{new}}, \mathcal{M}_{\text{old}})}{\phi(x'_{\text{new}}|x'_{\text{core}}, \mathcal{M}_{\text{old}}, \mathcal{M}_{\text{new}})} e^{-\Delta S_{\text{delete}}[x \to x'|\mathcal{M}_{\text{old}}]} && (29) \\ &= \frac{e^{-u(x''_{\text{core}}, x''_{\text{new}}, \mathcal{M}_{\text{new}}) + g(\mathcal{M}_{\text{new}})}}{e^{-u(x_{\text{core}}, x_{\text{old}}, \mathcal{M}_{\text{old}}) + g(\mathcal{M}_{\text{old}})}} \frac{P(\mathcal{M}_{\text{old}}|\mathcal{M}_{\text{new}})}{P(\mathcal{M}_{\text{new}}|\mathcal{M}_{\text{old}})} \frac{\phi(x'_{\text{old}}|x'_{\text{core}}, \mathcal{M}_{\text{new}}, \mathcal{M}_{\text{old}})}{\phi(x'_{\text{new}}|x'_{\text{core}}, \mathcal{M}_{\text{old}}, \mathcal{M}_{\text{new}})} \\ &\times e^{-w_{\text{insert}}[x' \to x''|\mathcal{M}_{\text{new}}]} \frac{e^{-u(x'_{\text{core}}, x'_{\text{new}}; \mathcal{M}_{\text{new}}, \lambda=0)}}{e^{-u(x''_{\text{core}}, x''_{\text{new}}; \mathcal{M}_{\text{new}}, \lambda=1)}} e^{-w_{\text{delete}}[x \to x'|\mathcal{M}_{\text{old}}]} \frac{e^{-u(x_{\text{core}}, x_{\text{old}}; \mathcal{M}_{\text{old}}, \lambda=1)}}{e^{-u(x'_{\text{core}}, x'_{\text{old}}; \mathcal{M}_{\text{old}}, \lambda=0)}} && (30) \\ &= \frac{e^{g(\mathcal{M}_{\text{new}})}}{e^{g(\mathcal{M}_{\text{old}})}} \frac{P(\mathcal{M}_{\text{old}}|\mathcal{M}_{\text{new}})}{P(\mathcal{M}_{\text{new}}|\mathcal{M}_{\text{old}})} \frac{\phi(x'_{\text{old}}|x'_{\text{core}}, \mathcal{M}_{\text{new}}, \mathcal{M}_{\text{old}})}{\phi(x'_{\text{new}}|x'_{\text{core}}, \mathcal{M}_{\text{old}}, \mathcal{M}_{\text{new}})} e^{-w_{\text{insert}}[x' \to x''|\mathcal{M}_{\text{new}}]} e^{-w_{\text{delete}}[x \to x'|\mathcal{M}_{\text{old}}]} \\ &\times \frac{e^{-u(x''_{\text{core}}, x''_{\text{new}}, \mathcal{M}_{\text{new}})}}{e^{-u(x''_{\text{core}}, x''_{\text{new}}; \mathcal{M}_{\text{new}}, \lambda=1)}} \cdot \frac{e^{-u(x_{\text{core}}, x_{\text{old}}; \mathcal{M}_{\text{old}}, \lambda=1)}}{e^{-u(x_{\text{core}}, x_{\text{old}}, \mathcal{M}_{\text{old}})}} \cdot \frac{e^{-u(x'_{\text{core}}, x'_{\text{new}}; \mathcal{M}_{\text{new}}, \lambda=0)}}{e^{-u(x'_{\text{core}}, x'_{\text{old}}; \mathcal{M}_{\text{old}}, \lambda=0)}} && (31)\end{aligned}$$

SAMPLING SCHEME IMPLEMENTATION

Hybrid scheme

Implementation

We break the **hybrid** acceptance criteria (Eq. 25) into the following components:

- The **stationary probability** from the initial and final chemical states, which is computed in the `ExpandedEnsembleSampler`:

$$\begin{aligned}\log \mathsf{P}_{\text{stationary}} &= \log \frac{e^{-u(x'_{\text{core}}, x'_{\text{new}}, \mathcal{M}_{\text{new}}) + g(\mathcal{M}_{\text{new}})}}{e^{-u(x_{\text{core}}, x_{\text{old}}, \mathcal{M}_{\text{old}}) + g(\mathcal{M}_{\text{old}})}} && (32) \\ &= \log \mathsf{P}_{\text{final}} - \log \mathsf{P}_{\text{initial}} && (33)\end{aligned}$$

  which we further decompose into the **initial** and **final** log probabilities of chemical states:

$$\begin{aligned}\log \mathsf{P}_{\text{final}} &= -u(x'_{\text{core}}, x'_{\text{new}}, \mathcal{M}_{\text{new}}) + g(\mathcal{M}_{\text{new}}) && (34) \\ \log \mathsf{P}_{\text{initial}} &= -u(x_{\text{core}}, x_{\text{old}}, \mathcal{M}_{\text{old}}) + g(\mathcal{M}_{\text{old}}) && (35)\end{aligned}$$

- The **chemical proposal probabilities**, which are computed by the `ProposalEngine`:

$$\log \mathsf{P}_{\text{chemical}} = \log \frac{P(\mathcal{M}_{\text{old}}|\mathcal{M}_{\text{new}})}{P(\mathcal{M}_{\text{new}}|\mathcal{M}_{\text{old}})} \tag{36}$$

- The **geometry proposal probabilities**, computed by the `GeometryEngine`:

$$\begin{aligned}\log \mathsf{P}_{\text{geometry}} &= \log \frac{\phi(x'_{\text{old}}|x'_{\text{core}}, \mathcal{M}_{\text{new}}, \mathcal{M}_{\text{old}})}{\phi(x_{\text{new}}|x_{\text{core}}, \mathcal{M}_{\text{old}}, \mathcal{M}_{\text{new}})} && (37) \\ &= \log \mathsf{P}_{\text{reverse}} - \log \mathsf{P}_{\text{forward}} && (38)\end{aligned}$$

  which we further decompose into **reverse** and **forward** geometry proposal probabilities:

$$\begin{aligned}\log \mathsf{P}_{\text{reverse}} &= \log \phi(x'_{\text{old}}|x'_{\text{core}}, \mathcal{M}_{\text{new}}, \mathcal{M}_{\text{old}}) && (39) \\ \log \mathsf{P}_{\text{forward}} &= \log \phi(x_{\text{new}}|x_{\text{core}}, \mathcal{M}_{\text{old}}, \mathcal{M}_{\text{new}}) && (40)\end{aligned}$$

  and finally the **NCMC** component, computed by the

`NCMCEngine`:

$$\log \mathsf{P}_{\mathrm{NCMC}} = \log e^{-\Delta S[x \to x' | \mathcal{M}_{\mathrm{old}} \to \mathcal{M}_{\mathrm{new}}]} \tag{41}$$

$$= \log \left[e^{-w[x \to x' | \lambda = 0 \to 1]} \frac{e^{-u(x, \lambda=0)}}{e^{-u(x', \lambda=1)}} \right] \tag{42}$$

$$= \log \mathsf{P}_{\mathrm{work}} + \log \mathsf{P}_{\mathrm{energy}} \tag{43}$$

which we further decompose into **work** and **energy** change contributions

$$\log \mathsf{P}_{\mathrm{work}} = -w[x \to x' | \lambda = 0 \to 1] \tag{44}$$

$$\log \mathsf{P}_{\mathrm{energy}} = u(x', \lambda = 1) - u(x, \lambda = 0) \tag{45}$$

JDC: Check that the energy component here is really the reduced potential for both GHMC and VV, rather than the total reduced energy.

With this definition of terms, the overall acceptance probability is therefore given as

$$\begin{aligned} \log \mathsf{P}_{\mathrm{accept}} &= \log \mathsf{P}_{\mathrm{final}} - \log \mathsf{P}_{\mathrm{initial}} + \log \mathsf{P}_{\mathrm{chemical}} \\ &+ \log \mathsf{P}_{\mathrm{reverse}} - \log \mathsf{P}_{\mathrm{forward}} \\ &+ \log \mathsf{P}_{\mathrm{work}} + \log \mathsf{P}_{\mathrm{energy}} \end{aligned} \tag{46}$$

Testing

We use several kinds of tests to ensure that the quantities described above are computed correctly.

check_alchemical_null_elimination: This test ensures that the NCMC work is computed correctly by performing a *null transformation* in which the overall free energy change should be zero. We can show that the expectation of the exponentiated work should be given by the exponentiated free energy difference (due to Jarzynski [1]):

$$\begin{aligned} & E_{0\to1}[e^{-w[x\to x'|\lambda=0\to1]}] \\ &= \sum_{x_0 \cdots x_N} P_{0\to1}[x \to x'] e^{-w[x\to x'|\lambda=0\to1]} \\ &= \sum_{x_0 \cdots x_N} \pi_0(x_0) \left[\prod_{n=1}^{N} K_n(x_{n-1}, x_n) \right] e^{-\sum_{n=1}^{N} (u_n(x_n) - u_{n-1}(x_n))} \\ &= \sum_{x_0 \cdots x_N} \pi_0(x_0) \left[\prod_{n=1}^{N} K_n(x_{n-1}, x_n) \right] \prod_{n=1}^{N} \frac{q_n(x_n)}{q_{n-1}(x_n)} \\ &= \sum_{x_0 \cdots x_N} \pi_0(x_0) \left[\prod_{n=1}^{N} K_n(x_{n-1}, x_n) \right] \prod_{n=1}^{N} \frac{Z_n \pi_n(x_n)}{Z_{n-1} \pi_{n-1}(x_n)} \\ &= \frac{Z_N}{Z_0} \sum_{x_0 \cdots x_N} \pi_0(x_1) K_0(x_0, x_1) \left[\prod_{n=2}^{N} K_n(x_{n-1}, x_n) \right] \prod_{n=1}^{N} \frac{\pi_n(x_n)}{\pi_{n-1}(x_n)} \\ &= \frac{Z_N}{Z_0} \sum_{x_1 \cdots x_N} \pi_0(x_1) \frac{\pi_1(x_1)}{\pi_0(x_1)} \left[\prod_{n=2}^{N} K_n(x_{n-1}, x_n) \right] \prod_{n=1}^{N} \frac{\pi_n(x_n)}{\pi_{n-1}(x_n)} \\ &= \frac{Z_N}{Z_0} = e^{-(f_N - f_0)} = e^{-\Delta f_{0\to1}} \end{aligned} \tag{47}$$

We can test the $\log \mathsf{P}_{work}$ component using the one-sided EXP estimator

$$\Delta f_{0\to1} = -\log E_{0\to1} \left[\exp \log \mathsf{P}_{\mathrm{work}} \right] \tag{48}$$

Note that we are only testing the **work** contribution here. The differential path action ($\log \Delta S = \log \mathsf{P}_{\mathrm{work}} + \log \mathsf{P}_{\mathrm{energy}}$) obeys different statistics. [JDC: Is there a similar test we could apply to $\log \Delta S$?]

The EXP estimator can produce heavily biased estimates, making the uncertainty estimates unreliable [2], so instead use the bidirectional BAR estimator to estimate switches in both directions when possible [3]. This also ensures that the NCMC method obeys the correct symmetry relations when run forward and backward. In particular, the protocol must be *symmetric* unless additional corrections for selecting the same protocol and its time-reverse are included [4].

check_harmonic_oscillator_ncmc: The same principles as above, applied to a harmonic oscillator. This scheme tests only the `NCMCIntegrator`, rather than the whole `NCMCEngine`.

Two-stage scheme

Implementation

We break the **two-stage** acceptance criteria (Eq 31) into the following components:

- The **stationary probability** from the initial and final chemical states, which is computed in the `ExpandedEnsembleSampler`:

$$\log \mathsf{P}_{\mathrm{stationary}} = \log \frac{e^{-u(x''_{\mathrm{core}}, x''_{\mathrm{new}}, \mathcal{M}_{\mathrm{new}}) + g(\mathcal{M}_{\mathrm{new}})}}{e^{-u(x_{\mathrm{core}}, x_{\mathrm{old}}, \mathcal{M}_{\mathrm{old}}) + g(\mathcal{M}_{\mathrm{old}})}} \tag{49}$$

$$= \log \mathsf{P}_{\mathrm{final}} - \log \mathsf{P}_{\mathrm{initial}} \tag{50}$$

  which we further decompose into the **initial** and **final** log probabilities of chemical states:

$$\log \mathsf{P}_{\mathrm{final}} = -u(x''_{\mathrm{core}}, x''_{\mathrm{new}}, \mathcal{M}_{\mathrm{new}}) + g(\mathcal{M}_{\mathrm{new}}) \tag{51}$$

$$\log \mathsf{P}_{\mathrm{initial}} = -u(x_{\mathrm{core}}, x_{\mathrm{old}}, \mathcal{M}_{\mathrm{old}}) + g(\mathcal{M}_{\mathrm{old}}) \tag{52}$$

- The **chemical proposal probabilities**, which are computed by the `ProposalEngine`:

$$\log \mathsf{P}_{\mathrm{chemical}} = \log \frac{P(\mathcal{M}_{\mathrm{old}} | \mathcal{M}_{\mathrm{new}})}{P(\mathcal{M}_{\mathrm{new}} | \mathcal{M}_{\mathrm{old}})} \tag{53}$$

- The **geometry proposal probabilities**, computed by the `GeometryEngine`:

$$\log \mathsf{P}_{\mathrm{geometry}} = \log \frac{\phi(x'_{\mathrm{old}} | x'_{\mathrm{core}}, \mathcal{M}_{\mathrm{new}}, \mathcal{M}_{\mathrm{old}})}{\phi(x'_{\mathrm{new}} | x'_{\mathrm{core}}, \mathcal{M}_{\mathrm{old}}, \mathcal{M}_{\mathrm{new}})} \tag{54}$$

$$= \log \mathsf{P}_{\mathrm{reverse}} - \log \mathsf{P}_{\mathrm{forward}} \tag{55}$$

which we further decompose into **reverse** and **forward** geometry proposal probabilities:

$$\log \mathsf{P}_{\text{reverse}} = \log \phi(x'_{\text{old}}|x'_{\text{core}}, \mathcal{M}_{\text{new}}, \mathcal{M}_{\text{old}}) \quad (56)$$
$$\log \mathsf{P}_{\text{forward}} = \log \phi(x'_{\text{new}}|x'_{\text{core}}, \mathcal{M}_{\text{old}}, \mathcal{M}_{\text{new}}) \quad (57)$$

and finally the **NCMC** components, computed by the `NCMCEngine`, where there are now two stages (**delete** and **insert**):

$$\begin{aligned}
\log \mathsf{P}_{\text{delete}} &= \log e^{-\Delta S_{\text{delete}}[x \to x'|\mathcal{M}_{\text{old}}]} && (58)\\
&= \log \left[e^{-w_{\text{delete}}[x \to x'|\mathcal{M}_{\text{old}}]} \frac{e^{-u(x, \mathcal{M}_{\text{old}}, \lambda=1)}}{e^{-u(x', \mathcal{M}_{\text{old}}, \lambda=0)}} \right] \\
&= \log \mathsf{P}_{\text{delete work}} + \log \mathsf{P}_{\text{delete energy}} && (59)\\
\log \mathsf{P}_{\text{insert}} &= \log e^{-\Delta S_{\text{insert}}[x' \to x'|\mathcal{M}_{\text{new}}]} && (60)\\
&= \log \left[e^{-w_{\text{insert}}[x' \to x''|\mathcal{M}_{\text{new}}]} \frac{e^{-u(x', \mathcal{M}_{\text{new}}, \lambda=0)}}{e^{-u(x'', \mathcal{M}_{\text{new}}, \lambda=1)}} \right] \\
&= \log \mathsf{P}_{\text{insert work}} + \log \mathsf{P}_{\text{insert energy}} && (61)
\end{aligned}$$

which we further decompose into **work** and **energy** change contributions for the separate **delete** and **insert** NCMC stages:

$$\begin{aligned}
\log \mathsf{P}_{\text{delete work}} &= -w_{\text{delete}}[x \to x'|\mathcal{M}_{old}] && (62)\\
\log \mathsf{P}_{\text{delete energy}} &= u(x', \mathcal{M}_{\text{old}}, \lambda = 0) - u(x, \mathcal{M}_{\text{old}}, \lambda = 1) \\
\log \mathsf{P}_{\text{insert work}} &= -w_{\text{insert}}[x' \to x''|\mathcal{M}_{new}] && (63)\\
\log \mathsf{P}_{\text{insert energy}} &= u(x'', \mathcal{M}_{\text{new}}, \lambda = 1) - u(x', \mathcal{M}_{\text{new}}, \lambda = 0)
\end{aligned}$$

JDC: Check that the energy component here is really the reduced potential for both GHMC and VV, rather than the total reduced energy. ski

With this definition of terms, the overall acceptance probability is therefore given as

$$\begin{aligned}
\log \mathsf{P}_{\text{accept}} &= \log \mathsf{P}_{\text{final}} - \log \mathsf{P}_{\text{initial}} + \log \mathsf{P}_{\text{chemical}} \\
&+ \log \mathsf{P}_{\text{delete work}} + \log \mathsf{P}_{\text{delete energy}} \\
&+ \log \mathsf{P}_{\text{reverse}} - \log \mathsf{P}_{\text{forward}} \\
&+ \log \mathsf{P}_{\text{insert work}} + \log \mathsf{P}_{\text{insert energy}} \quad (64)
\end{aligned}$$

ACKNOWLEDGMENTS

We are grateful to many people. JDC acknowledges a Louis V. Gerstner Young Investigator Award, NIH core grant P30-CA008748, and the Sloan Kettering Institute for funding during the course of this work.

[1] C. Jarzynski, Phys. Rev. Lett. **78**, 2690 (1997).
[2] M. R. Shirts and V. S. Pande, J. Chem. Phys. **122**, 144107 (2005).
[3] C. H. Bennett, J. Comput. Phys. **22**, 245 (1976).
[4] J. P. Nilmeier, G. E. Crooks, D. D. L. Minh, and J. D. Chodera, Proc. Natl. Acad. Sci. USA **108**, E1009 (2011).