Supporting information for: w-REXAMD: A Hamiltonian replica exchange approach to improve free energy calculations for systems with kinetically-trapped conformations

Mehrnoosh Arrar,*† Cesar Augusto F. de Oliveira,†‡ Mikolai Fajer,† William Sinko,¶ and J. Andrew McCammon†‡

Department of Chemistry and Biochemistry, University of California San Diego, La Jolla, California 92093-0365, Howard Hughes Medical Institute, University of California San Diego, La Jolla, California 92093-0365, and Biomedical Sciences Program, University of California San Diego, La Jolla, California 92093-0365

E-mail: marrar@ucsd.edu

*To whom correspondence should be addressed
†Department of Chemistry and Biochemistry, University of California San Diego, La Jolla, California 92093-0365
‡Howard Hughes Medical Institute, University of California San Diego, La Jolla, California 92093-0365
¶Biomedical Sciences Program, University of California San Diego, La Jolla, California 92093-0365
1 Supplemental Computational Details

1.1 Accelerated MD Approach

The windowed aMD equation (Equation 1) was recently introduced\(^1\) and we will summarize it here.

\[
V^*(r) = \begin{cases} 
V(r) - \Delta V^c(r) & V(r) > E_1 \\
V(r) & V(r) \leq E_1
\end{cases}
\]  

(1)

where

\[
\Delta V^c(r) = \frac{(V(r) - E_1)^2}{(\alpha_1 + V(r) - E_1) \left(1 + \exp\left(\frac{V(r) - E_2}{\alpha_2}\right)\right)}
\]  

(2)

When the potential energy \(V(r)\) is higher than a fixed threshold \(E_1\), it is lowered by \(\Delta V^c(r)\), allowing the simulation to sample conformations according to the modified Hamiltonian \(V^*(r)\). The parameter \(E_2\) creates a window of acceleration, protecting high barriers since \(\Delta V^c(r) \to 0\) when \(V(r) \gg E_2\). In this way it is possible to smooth the roughness of the potential energy surface, but avoid increased sampling of high energy conformations. The \(\alpha\) parameters tune the transitions between modified and real potential energy surfaces. Although this approach could be used to accelerate according to total potential energy, in this work only the torsional potential energy was modified.

1.2 Hamiltonian Replica Exchange

Each thermodynamic state in the w-REXAMD simulation corresponds to a set of four parameters \((E_1, E_2, \alpha_1, \alpha_2)\) that determine the degree of acceleration of a replica at that state. Four replicas were used in each simulation, and the least accelerated state was always the unmodified Hamiltonian. Neighbor exchanges were attempted every 300 MD steps (0.3 ps).

Selection of Parameters. We chose the parameters for the set of replicas empirically. We used the average dihedral energy from a 1ns conventional MD simulation (cMD) of butane in water as a
benchmark for $E_1$ and tested values for $E_2$ which were multiples of the maximum dihedral energy in the cMD simulation. We then did a series of short w-aMD simulations with $\alpha_2 = 1$ kcal/mol, which is approximately $0.2 \times (E_2 - E_1)$ and varied $\alpha_1$ from low to high acceleration: 1, 0.5, and 0.1 kcal/mol. The choice of parameters was made by analyzing both the distributions of $\Delta V^c$ and the dihedral angle sampling in each simulation. This process was repeated for cyclohexane. For bromocyclohexane the sum of the dihedral energy of the common atoms, and both initial and final states’ soft-core atoms was used to determine the acceleration parameters. Table 1 summarizes the parameters used. The w-REXAMD simulations were performed using a modified version of the AMBER11 sander module. The alchemical transformations were done using a python wrapper and a modified AMBER10 source code.

Table 1: Summary table of acceleration parameters

|            | $E_1$ (kcal/mol) | $E_2$ (kcal/mol) | $\alpha_1$ (kcal/mol) | $\alpha_2$ (kcal/mol) |
|------------|-----------------|-----------------|-----------------------|-----------------------|
| Butane     | 1.0             | 5               | 1, 0.5, 0.1           | 1                     |
| Cyclohexane| 3.5             | 15              | 1, 0.5, 0.1           | 1                     |
| Bromocyclohexane | 8.0 | 50              | 1, 0.5, 0.1           | 1                     |

**MD Details.** All three molecules were built using the GAFF force field, with HF/6-31G* RESP charges obtained using Gaussian 03. Antechamber was used to prepare the molecules and LEaP was used to solvate them. The systems were solvated in 10.0 angstrom TIP3P water boxes (ff99SB force field) which were first heated to 300 K and equilibrated until the the correct density of water at 1 atm was reached. Pressure was kept constant during equilibration using the Berendsen barostat. The simulations were then simulated in the NVT ensemble with temperature regulated using the Anderson thermostat; velocities were randomized every 1000 steps. A 1 fs time-step was used. An 8.0 Angstrom cutoff was used for non-bonded interactions.

The w-REXAMD simulations were compared to identical replica exchange simulations in which all replicas were run on the unmodified Hamiltonian (simulations are called REGREX). This way any improvement in sampling is separated from the advantage of running multiple trajectories in parallel. In the REGREX simulations, the four cMD trajectories exchanged at every attempt.
1.3 Thermodynamic Integration

All atoms being coupled or decoupled according to the value of the parameter \( \lambda \) were treated with soft-core potentials.\(^9\) Because of the implementation of the soft-core potential in the AMBER sander module, no simulations were done at \( \lambda = 0.0 \) or \( \lambda = 1.0 \). Nine evenly spaced lambda points \([0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9]\) were used, and 1.5ns (5000 frames saved) of REGREX and w-REXAMD was run at each lambda point, after an equilibration period of 150 ps.

We used thermodynamic integration to calculate the change in free energy between initial and final states:

\[
\Delta G_{0\rightarrow1} = \int_{0}^{1} d\lambda \langle \frac{\delta V}{\delta \lambda} \rangle_{\lambda}
\]

The integral in (3) was evaluated using the trapezoid rule:

\[
\Delta G \approx \langle \frac{\delta V}{\delta \lambda} \rangle_{\lambda_1} \lambda_1 + \frac{1}{2} \sum_{i=2}^{N} \left[ \langle \frac{\delta V}{\delta \lambda} \rangle_{\lambda_i} + \langle \frac{\delta V}{\delta \lambda} \rangle_{\lambda_{i-1}} \right] (\lambda_i - \lambda_{i-1}) + \langle \frac{\delta V}{\delta \lambda} \rangle_{\lambda_N} (1 - \lambda_N)
\]

We calculated \( \langle \frac{\delta V}{\delta \lambda} \rangle_{\lambda_i} \) as the average:

\[
\langle \frac{\delta V}{\delta \lambda} \rangle_{\lambda_i} = \frac{1}{N_i} \sum_{n} \frac{\delta V}{\delta \lambda_{i,n}}
\]

where \( N_i \) is the number of configurations in a state trajectory from a simulation at \( \lambda_i \). Because the series of \( N_i \frac{\delta V}{\delta \lambda_{i,n}} \) values may be correlated, we approximated the statistical uncertainty \( \delta^2 \langle \frac{\delta V}{\delta \lambda} \rangle_{\lambda_i} \) at each \( \lambda_i \) as described by Chodera et al.:\(^{10}\)

\[
\delta_{\lambda_i}^2 = \frac{\sigma^2}{N_i/g}
\]

where \( \sigma^2 \) is the variance of the \( \frac{\delta V}{\delta \lambda} \) series, and \( g \) is the statistical inefficiency, which incorporates the integrated autocorrelation time \( \tau \):

\[
g = 1 + 2\tau
\]
The error propagation formula was used with eq 4 to calculate the variance for the free energy change of the transformation. We repeated the bromocylohexane self transformation in triplicate and estimate the free energy change $\Delta \tilde{G}$ as the average of the three independent $\Delta G_j$ values, weighted by their associated statistical uncertainty $\delta_j^2$.

$$\Delta \tilde{G} = \frac{\sum_j \Delta G_j w_j}{\sum w_j}$$  \hspace{1cm} (8)

where $w_i = \frac{1}{\delta_i^2}$, and the uncertainty of the weighted average $\Delta \tilde{G}$ is

$$\sigma = \frac{1}{\sqrt{\sum w_j}}$$  \hspace{1cm} (9)

2 Supplemental Figures

Figure 1: Convergence of chair 1 (blue) and chair 2 (red) fraction occupancies in unaccelerated state of w-REXAMD simulations (5ns total). Error bars show standard deviation from three independent simulations.
Table 2: Summary table of mixing among states in replica exchange simulations. Mean-first passage times from each state to either the most accelerated state ($\tau_{state3}$) or down to the unaccelerated state ($\tau_{unaccelerated}$) in w-REXAMD alchemical self-transformation of bromocyclohexane. Error indicates 90% confidence interval.

| State                  | $\tau_{state3}$ (exchange attempts) | $\tau_{unaccelerated}$ (exchange attempts) |
|------------------------|-------------------------------------|--------------------------------------------|
| Unaccelerated state    | 9.610 ± 0.713                       | -                                          |
| State 1                | 3.688 ± 0.063                       | 3.561 ± 0.107                              |
| State 2                | 2.158 ± 0.020                       | 5.159 ± 0.149                              |
| State 3                | -                                   | 6.729 ± 0.193                              |
References

[1] Sinko, W.; de Oliveira, C. A. F.; Pierce, L. C. T.; McCammon, J. A. *J Chem Theory Comput* 2011, 8, 17–23.

[2] Case, D. A.; Darden, T. A.; Cheatham, T. E.; III.; Simmerling, C. L.; Wang, J.; Duke, R. E.; Luo, R.; Walker, R. C.; Zhang, W.; Merz, K. M.; Roberts, B. P.; Wang, B.; Hayik, S.; Roitberg, A.; Seabra, G.; Kolossvai, I.; Wong, K. F.; Paesani, F.; Vanicek, J.; Liu, J.; Wu, X.; Brozell, S. R.; Steinbrecher, T.; Gohlke, H.; Cai, Q.; Ye, X.; Wang, J.; Hsieh, M. J.; Cui, G.; Roe, D. R.; Mathews, D. H.; Seetin, M. G.; Sagui, C.; Babin, V.; Luchko, T.; Gusarov, S.; Kovalenko, A.; Kollman, P. A. *University of California, San Francisco* 2010.

[3] Wang, J.; Wolf, R. M.; Caldwell, J. W.; Kollman, P. A.; Case, D. A. *J Comput Chem* 2004, 25, 1157–1174.

[4] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Laham, A. M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. 2003,

[5] Tan, C.; Tan, Y.-H.; Luo, R. *J Phys Chem B* 2007, 111, 12263–12274.
[6] Hornak, V.; Abel, R.; Okur, A.; Strockbine, B.; Roitberg, A.; Simmerling, C. *Proteins* **2006**, 65, 712–725.

[7] Berendsen, H.; Postma, J. *J. Chem. Phys.* **1984**, 81, 3684–3690.

[8] Andersen, H. C. *J. Chem. Phys.* **1980**, 72, 2384–2393.

[9] Zacharias, M.; Straatsma, T. P.; McCammon, J. A. *J. Chem. Phys.* **1994**, 100, 9025–9031.

[10] Chodera, J. D.; Swope, W. C.; Pitera, J. W.; Seok, C.; Dill, K. A. *J Chem Theory Comput* **2007**, 3, 26–41.