Driven Metadynamics: Reconstructing Equilibrium Free Energies from Driven Adaptive-Bias Simulations (Supporting Information)

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Asymptotic Convergence of Driven Metadynamics

Suppose that we iterate the Driven Metadynamics protocol (as described in the main text) until the adaptive term of the biasing potential converges to $U_a(x,t\to\infty)\approx U_a^s(x)+u(t)$. Assuming $\dot{u}(t)$ is small, the system at this point can be considered as a nonequilibrium driven system governed by the Hamiltonian $H(\mathbf{r},\mathbf{p})+U_a^s(x)+U_d(x,t)$. Assuming there is a unique converged $U_a^s(x)$ (as will be verified), we can construct a driven ensemble using the iterations performed after the convergence. Having multiple independent runs, one may also use all the nearly converged trajectories to construct this ensemble. One can use the nonequilibrium work relation (3) to reconstruct the free energy of the biased system, $F^s(x)=F(x)+U_a^s(x)$ (up to an additive constant):

$$\mathrm{e}^{-\beta F^s(x)}\propto\left\langle\delta(x-x^t)\,\mathrm{e}^{-\beta\Delta w^t}\right\rangle_{da}, \tag{S1}$$

If we replace the kernel with the δ function in relation (4), we have

$$\left\langle\dot{U}_a(x,t)\right\rangle_{da}=\left\langle\omega(x,t)\,\delta(x-x^t)\,\mathrm{e}^{-\beta\Delta w^t}\right\rangle_{da}. \tag{S2}$$

Once a convergence is reached we have $\omega(x,t)\approx\omega^s(x)$ and

$$\left\langle\dot{U}_a(x,t)\right\rangle_{da}=\omega^s(x)\left\langle\delta(x-x^t)\,\mathrm{e}^{-\beta\Delta w^t}\right\rangle_{da}. \tag{S3}$$

Using the nonequilibrium work relation (S1), we can conclude that:

$$\left\langle\dot{U}_a(x,t)\right\rangle_{da}\propto\omega^s(x)\mathrm{e}^{-\beta F^s(x)}. \tag{S4}$$

If $\omega^s(x)\propto\exp(-\beta' U_a^s(x))$ (well-tempered rate) this relation implies $U_a^s(x)=-(1+\frac{\beta'}{\beta})^{-1}F(x)$ and if $\omega^s(x)$ does not depend on x ($\beta'\to 0$ limit), this relation implies $U_a^s(x)=-F(x)$. Relation (S4) and its implications are reminiscent of non-driven metadynamics[1] and show that the adaptive term of the potential averaged over a D-MetaD ensemble converges to the same expression as that of its

non-driven counterpart. It also shows that the assumption we made above regarding the uniqueness of $U_a^s(x)$ is valid.

It has been shown[2] that nonequilibrium work relations are valid not only for Markovian (*i.e.*, memory-less) processes but also for history-dependent ones[2] as long as there exists a unique stationary state for each $X(\tau)$ ($0 \leq \tau \leq T$) when $X(\tau)$ is not varied by time t (*i.e.*, ergodicity assumption). If we perform a large number of independent driven metadynamics simulations, we can argue $\left\langle U_a(x,t)\right\rangle_{da}$ is equal to $\left\langle U_a(x,t)\right\rangle_{\tau}$ in which $\left\langle .\right\rangle_{\tau}$ denotes an average over the steady state ensemble associated with $X(\tau)$. Interestingly, if the target $X(\tau)$ is fixed (*i.e.*, independent of t), D-MetaD becomes a non-driven metadynamics with a constraint $U_d(x,\tau) = \frac{k}{2}(x - X(\tau))^2$ and a history-dependent bias $U_a(x,t)$ in which $\left\langle \dot{U}_a(x,t)\right\rangle_{\tau}$ is

$$\left\langle \omega(x^t,t)\, K(x^t - x)\, \mathrm{e}^{-\beta \Delta w^t}\right\rangle_{\tau} = \left\langle \omega(x^t,t)\, K(x^t - x)\, \mathrm{e}^{\beta U_d(x^t,\tau)}\right\rangle_{\tau}. \tag{S5}$$

In the steady state, $p(x,t)$ is proportional to $\exp(-\beta(F(x) + U_a^s(x) + U_d(x,\tau)))$ thus assuming the kernel approximates a δ function, $\left\langle \dot{U}_a(x,t)\right\rangle_{\tau}$ converges to $\omega^s(x)\exp(-\beta(F(x) + U_a^s(x)))$ in which $U_a^s(x)$ is independent of $X(\tau)$.

Note that although $\left\langle .\right\rangle_{da}$ denotes an ensemble average, if we only have one iterative simulation, $U_a(x,t)$ averaged over these iterations can be considered equivalent to $\left\langle U_a(x,t)\right\rangle_{da}$ above when $t \to \infty$, assuming ergodicity. However, the sampling can be improved in a "multiple-walker" scheme in which several systems share the same adaptive potential which can be approximated as:

$$U_a(x,t) = \int_0^t dt'\, \omega(x,t') \left\langle \delta(x - x^{t'})\, \mathrm{e}^{-\beta \Delta w^{t'}}\right\rangle_{da}, \tag{S6}$$

if we replace the δ function with the kernel function. Using the nonequilibrium work relation (S1), one can connect this ensemble to a non-driven one:

$$U_a(x,t) = \int_0^t dt'\, \omega(x,t') \left\langle \delta(x - x^{t'})\right\rangle_{a}. \tag{S7}$$

This is the multiple-walker extension of metadynamics.[3] Therefore, $U_a(x,t)$ in a multiple-walker driven adaptive-bias system is equivalent to that of a multiple-walker non-driven adaptive-bias system, given sufficient number of walkers. Note that the two systems may behave very differently initially, but they will converge to the same adaptive potential term.

References

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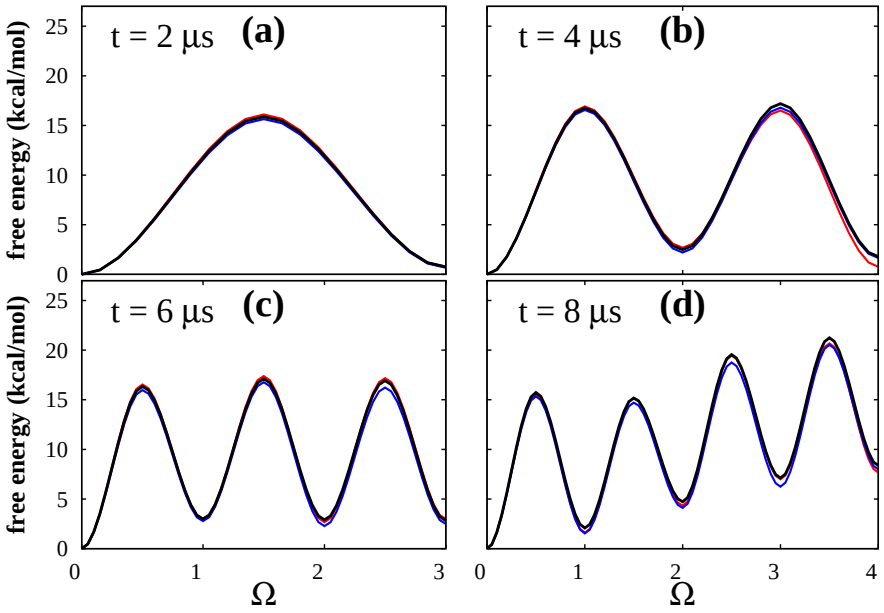

Figure S1: Converged free energy profile $F(\Omega)$ (offset by $F(0)$) obtained from SMD (red), MetaD (blue), and D-MetaD (black) simulations of **(a)** monomeric, **(b)** dimeric, **(c)** trimeric, and **(d)** tetrameric polyproline peptides.

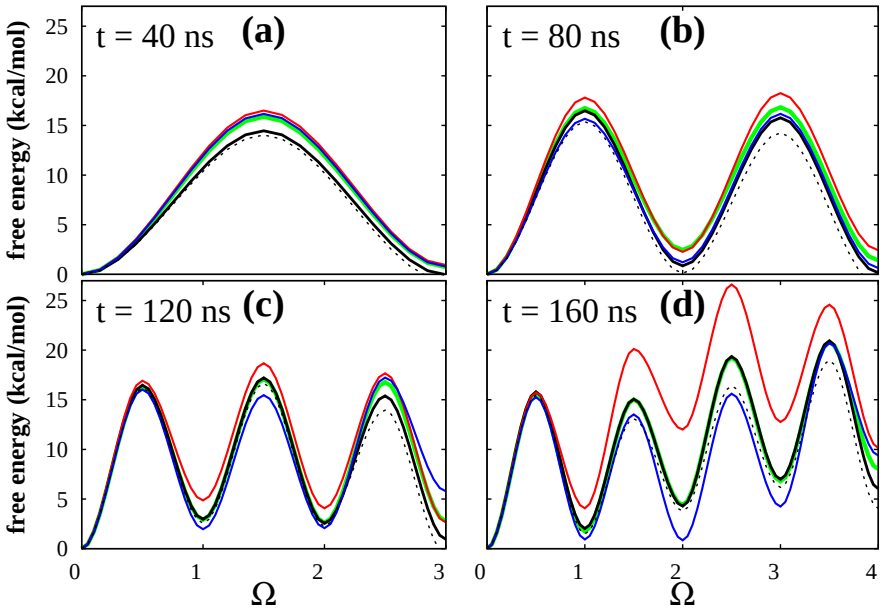

Figure S2: Free energy profile $F(\Omega)$ (offset by $F(0)$) obtained from $t = 40 \times n$ ns (*i.e.*, equivalent of 200 bidirectional iterations) of SMD (red), MetaD (blue), and D-MetaD (black) simulations on a n-meric peptide with **(a)** $n = 1$, **(b)** $n = 2$, **(c)** $n = 3$, and **(d)** $n = 4$. The dashed curves are the D-MetaD results without the work-based corrections (*i.e.*, $F_U(\Omega)$) and the green curves are the average of the three converged curves in Fig. S1 (*i.e.*, $F_c(\Omega)$). The superior efficiency of the D-MetaD method becomes evident in longer peptides due to its scalability.