

Bias forces in well-tempered metadynamics

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1. Single CV

According to well-tempered metadynamics [1], bias potential (V_{bias}) deposited at any time (t) along a single collective variable (CV) with respect to CV at every iteration (n_{iter}),

$$V_{\text{bias}}(\text{CV}, t_{\text{niter}})_{\text{CV}_t} = V_{\text{bias}}(\text{CV}, t_{\text{niter}-1})_{\text{CV}_t} + w \times \exp \left\{ -\frac{1}{2} \left(\frac{(\text{CV} - \text{CV}_{\text{niter}})}{\sigma} \right)^2 \right\}_{\text{CV}_t}$$

- In standard metadynamics [2], $w = w_0$
- In well-tempered metadynamics [1], $w = w_0 \times \exp \left(-\frac{V_{\text{bias}}(\text{CV}, t_{\text{niter}})}{k_B \Delta T} \right)$

Force at every timestep (t) due to deposited bias potential:

$$F_{\text{bias}}(\mathbf{r}, t) = - \left\{ \frac{dV_{\text{bias}}(\text{CV}, t_{\text{niter}})}{d\text{CV}} \right\}_{\text{CV}_t} \times \frac{d\text{CV}}{d\mathbf{r}_t}$$

Substituting $V_{\text{bias}}(\text{CV}, t_{\text{niter}})$ in the first term of the RHS in the above equation

$$\left\{ \frac{dV_{\text{bias}}(\text{CV}, t_{\text{niter}})}{d\text{CV}} \right\}_{\text{CV}_t} = \left\{ \frac{d \left[V_{\text{bias}}(\text{CV}, t_{\text{niter}-1}) + w \times \exp \left\{ -\frac{1}{2} \left(\frac{(\text{CV} - \text{CV}_{\text{niter}})}{\sigma} \right)^2 \right\} \right]}{d\text{CV}} \right\}_{\text{CV}_t}$$

- Helper function: Derivative of Gaussian at any iteration

$$\begin{aligned} & \left\{ \frac{d \left[w \times \exp \left\{ -\frac{1}{2} \left(\frac{(\text{CV} - \text{CV}_{\text{niter}})}{\sigma} \right)^2 \right\} \right]}{d\text{CV}} \right\}_{\text{CV}_t} \\ &= \left\{ -w \times \frac{(\text{CV} - \text{CV}_{\text{niter}})}{\sigma^2} \exp \left\{ -\frac{1}{2} \left(\frac{(\text{CV} - \text{CV}_{\text{niter}})}{\sigma} \right)^2 \right\} \right\}_{\text{CV}_t} \end{aligned}$$

Substituting helper function in $\left\{ \frac{dV_{\text{bias}}(\text{CV}, t_{\text{niter}})}{d\text{CV}} \right\}_{\text{CV}_t}$

$$\left\{ \frac{dV_{\text{bias}}(CV, t_{\text{niter}})}{dCV} \right\}_{CV_i} =$$

$$\left\{ \sum_{\text{iter} \leq \text{niter}-1} \left[-w \times \frac{(CV - CV_{\text{niter}})}{\sigma^2} \exp \left\{ -\frac{1}{2} \left(\frac{(CV - CV_{\text{niter}})}{\sigma} \right)^2 \right\} \right] \right.$$

$$\left. -w \times \frac{(CV - CV_{\text{niter}})}{\sigma^2} \exp \left\{ -\frac{1}{2} \left(\frac{(CV - CV_{\text{niter}})}{\sigma} \right)^2 \right\} \right\}_{CV_i}$$

2. N CVs

Bias potential every n number of iterations (niter):

$$V_{\text{bias}}(CV_1, CV_2, \dots, CV_n, t_{\text{niter}})_{CV_{1,t}, CV_{2,t}, \dots, CV_{n,t}}$$

$$= V_{\text{bias}}(CV_1, CV_2, \dots, CV_n, t_{\text{niter}-1})_{CV_{1,t}, CV_{2,t}, \dots, CV_{n,t}}$$

$$+ w \times \prod_{i=1..N} \exp \left\{ -\frac{1}{2} \left(\frac{(CV_i - CV_{i, \text{niter}})}{\sigma_i} \right)^2 \right\}_{CV_{i,t}}$$

- In standard metadynamics, $w = w_0$
- In well-tempered metadynamics, $w = w_0 \times \exp \left(-\frac{V_{\text{bias}}(CV_1, CV_2, \dots, CV_n, t_{\text{niter}})}{k_B \Delta T} \right)_{CV_{1, \text{niter}}, CV_{2, \text{niter}}, \dots, CV_{n, \text{niter}}}$

Force at every timestep due to bias potential:

$$F_{\text{bias}}(t) = - \sum_{i=1..N} \left\{ \frac{dV_{\text{bias}}(CV_1, CV_2, \dots, CV_n, t_{\text{niter}})}{dCV_i} \right\}_{CV_{i,t}} \times \frac{dCV_i}{dr_t}$$

Substituting $V_{\text{bias}}(CV_1, CV_2, C_{\text{niter}})$ in the first term of the RHS of $F_{\text{bias}}(t)$

$$\left\{ \frac{dV_{\text{bias}}(CV_1, CV_2, \dots, CV_n, t_{\text{niter}})}{dCV_i} \right\}_{CV_{i,t}} =$$

$$\left\{ \frac{d \left[V_{\text{bias}}(CV_1, CV_2, \dots, CV_n, t_{\text{niter}-1}) + w \times \prod_{i=1..N} \exp \left\{ -\frac{1}{2} \left(\frac{(CV_i - CV_{i, \text{niter}})}{\sigma_i} \right)^2 \right\} \right]}{dCV_i} \right\}_{CV_{i,t}}$$

- Helper function: Derivative of Gaussian (gDerv) with respect to CV_1 at any iteration

$$\begin{aligned}
& \left\{ \frac{d \left[w \times \prod_{i=1..N} \exp \left\{ -\frac{1}{2} \left(\frac{(CV_i - CV_{i, niter})}{\sigma_i} \right)^2 \right\} \right]}{dCV_1} \right\}_{CV_1, t} \\
&= \left\{ -w \times \frac{(CV_1 - CV_{1, niter})}{\sigma_1^2} \exp \left\{ -\frac{1}{2} \left(\frac{(CV_1 - CV_{1, niter})}{\sigma_1} \right)^2 \right\} \right. \\
&\quad \left. \times \prod_{i=2..N} \exp \left\{ -\frac{1}{2} \left(\frac{(CV_i - CV_{i, niter})}{\sigma_i} \right)^2 \right\} \right\}_{CV_{1,t}}
\end{aligned}$$

Substituting helper function in general case i.e., $\left\{ \frac{dV_{\text{bias}}(CV_1, CV_2, \dots, CV_n, t_{\text{niter}})}{dCV_i} \right\}_{CV_i, t}$

$$\begin{aligned}
& \left\{ \frac{dV_{\text{bias}}(CV_1, CV_2, \dots, CV_n, t_{\text{niter}})}{dCV_i} \right\}_{CV_i, t} = \\
& \left\{ \sum_{iter \leq niter-1} \left[-w \times \frac{(CV_i - CV_{i, niter})}{\sigma_i^2} \exp \left\{ -\frac{1}{2} \left(\frac{(CV_i - CV_{i, niter})}{\sigma_i} \right)^2 \right\} \right. \right. \\
& \quad \left. \times \prod_{j \neq i, j=1..N} \exp \left\{ -\frac{1}{2} \left(\frac{(CV_j - CV_{j, niter})}{\sigma_j} \right)^2 \right\} \right] \\
& \quad \left. -w \times \frac{(CV_i - CV_{i, niter})}{\sigma_i^2} \exp \left\{ -\frac{1}{2} \left(\frac{(CV_i - CV_{i, niter})}{\sigma_i} \right)^2 \right\} \right. \\
& \quad \left. \times \prod_{j \neq i, j=1..N} \exp \left\{ -\frac{1}{2} \left(\frac{(CV_j - CV_{j, niter})}{\sigma_j} \right)^2 \right\} \right\}_{CV_i, t}
\end{aligned}$$

Combining the two terms in RHS,

$$\begin{aligned}
& \left\{ \frac{dV_{\text{bias}}(CV_1, CV_2, \dots, CV_n, t_{\text{niter}})}{dCV_i} \right\}_{CV_i, t} = \\
& \left\{ \sum_{iter \leq niter} \left[-w \times \frac{(CV_i - CV_{i, niter})}{\sigma_i^2} \exp \left\{ -\frac{1}{2} \left(\frac{(CV_i - CV_{i, niter})}{\sigma_i} \right)^2 \right\} \right. \right. \\
& \quad \left. \times \prod_{j \neq i, j=1..N} \exp \left\{ -\frac{1}{2} \left(\frac{(CV_j - CV_{j, niter})}{\sigma_j} \right)^2 \right\} \right] \right\}_{CV_i, t}
\end{aligned}$$

In terms of gaussianDerv (gDerv) and gaussian (g),

$$\left\{ \frac{dV_{\text{bias}}(CV_1, CV_2, \dots, CV_n, t_{\text{niter}})}{dCV_i} \right\}_{CV_{i,t}}$$

$$= \left\{ \sum_{iter \leq niter} \left[w \times gDerv(CV_i - CV_{i,niter}, \sigma_i) \times \prod_{j \neq i, j=1..N} g(CV_i - CV_{i,niter}, \sigma_i) \right] \right\}_{CV_{i,t}}$$

[1] A. Barducci, G. Bussi, and M. Parrinello, *Well-Tempered Metadynamics: A Smoothly Converging and Tunable Free-Energy Method*, Physical Review Letters **100**, 020603 (2008).

[2] A. Laio and M. Parrinello, *Escaping Free-Energy Minima*, Proceedings of the National Academy of Sciences **99**, 12562 (2002).