Bias forces in well-tempered metadynamics

Siva Dasetty

Notes | 07.07.20

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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 every iteration ($niter$),

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

- 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:

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

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

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

- Helper function: Derivative of Gaussian at any iteration

$$\left\{\frac{d\left[w \times exp\left\{-\frac{1}{2}\left(\frac{(\text{CV}-\text{CV}_{\text{niter}})}{\sigma}\right)^2\right\}\right]}{\text{dCV}}\right\}_{CV_t}$$
$$= \left\{-w \times \frac{(CV - CV_{\text{niter}})}{\sigma^2} \exp\left\{-\frac{1}{2}\left(\frac{(CV - CV_{\text{niter}})}{\sigma}\right)^2\right\}\right\}_{CV_t}$$

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

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

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

3. N CVs

Bias potential every n number of iterations (niter):

$$V_{\text{bias}}\left(\text{CV}_1, \text{CV}_2, \ldots \text{CV}_n,\ t_{\text{niter}}\right)_{\text{CV}_{1,t}, \text{CV}_{2,t}, \ldots, \text{CV}_{n,t}}$$
$$= V_{\text{bias}}\left(\text{CV}_1, \text{CV}_2, \ldots \text{CV}_n, t_{niter-1}\right)_{\text{CV}_{1,t}, \text{CV}_{2,t}, \ldots, \text{CV}_{n,t}}$$
$$+ w \times \prod_{i=1..N}\exp\left\{-\frac{1}{2}\left(\frac{\left(\text{CV}_i - \text{CV}_{i,\ niter}\right)}{\sigma_i}\right)^2\right\}_{\text{CV}_{i,\ t}}$$

- In standard metadynamics, $w = w_0$
- In well-tempered metadynamics, $w = w_0 \times \exp\left(-\frac{V_{\text{bias}}\left(\text{CV}_1, \text{CV}_2, \ldots \text{CV}_n, t_{\text{niter}}\ \right)}{k_B \Delta T}\right)_{\text{CV}_{1,\ niter}, \text{CV}_{2,\ niter}, \ldots, \text{CV}_{n,niter}}$

Force at every timestep due to bias potential:

$$F_{\text{bias}}\left(t\right) = \ -\sum_{i=1,..N}\left\{\frac{dV_{\text{bias}}\left(CV_1, CV_2, \ldots CV_n, t_{\text{niter}}\right)}{\text{dCV}_i}\right\}_{CV_{i,t}} \times \frac{\text{dCV}_i}{\text{dr}_t}$$

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

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

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

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

$$\left\{\frac{d\left[w\times\prod_{i=1..N}\exp\left\{-\frac{1}{2}\left(\frac{(CV_i-CV_{i,\ niter})}{\sigma_i}\right)^2\right\}\right]}{\mathrm{dCV}_1}\right\}_{CV_{1,\ t}}$$

$$=\left\{-w\times\frac{(CV_1-CV_{1,niter})}{\sigma_1^2}\exp\left\{-\frac{1}{2}\left(\frac{(CV_1-CV_{1,\ niter})}{\sigma_1}\right)^2\right\}\right.$$
$$\left.\times\prod_{i=2..N}\exp\left\{-\frac{1}{2}\left(\frac{(CV_i-CV_{i,\ niter})}{\sigma_i}\right)^2\right\}\right\}_{CV_{1.t}}$$

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

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

$$\left\{\sum_{niter\leq niter-1}\left[-w\times\frac{(CV_i-CV_{i,niter})}{\sigma_i^2}\exp\left\{-\frac{1}{2}\left(\frac{(CV_i-CV_{i,\ niter})}{\sigma_i}\right)^2\right\}\right.\right.$$
$$\left.\times\prod_{j\neq i,j=1..N}\exp\left\{-\frac{1}{2}\left(\frac{(CV_i-CV_{i,\ niter})}{\sigma_i}\right)^2\right\}\quad\right]$$

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

Combining the two terms in RHS,

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

$$\left\{\sum_{niter\leq niter}\left[-w\times\frac{(CV_i-CV_{i,niter})}{\sigma_i^2}\exp\left\{-\frac{1}{2}\left(\frac{(CV_i-CV_{i,\ niter})}{\sigma_i}\right)^2\right\}\right.\right.$$
$$\left.\left.\times\prod_{j\neq i,j=1..N}\exp\left\{-\frac{1}{2}\left(\frac{(CV_i-CV_{i,\ niter})}{\sigma_i}\right)^2\right\}\quad\right]\right\}_{CV_{i,t}}$$

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

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

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

[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).