Metadynamics simulation versus OPES simulation and an example comparison

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1 Introduction

In molecular simulations, efficiently sampling the conformational space of complex systems remains a significant challenge due to the presence of high free energy barriers that trap the system in metastable states.If the barriers are significant larger than thermal fluctuation(K_BT). Enhanced sampling techniques have emerged as powerful tools to overcome these limitations by accelerating rare events while maintaining thermodynamic accuracy. Among these approaches, metadynamics[1][2] has established itself as a widely-used method that employs a history-dependent bias potential to explore free energy surfaces. This technique systematically discourages revisiting of previously sampled configurations through the addition of repulsive Gaussian potentials, enabling comprehensive exploration of the phase space.

More recently, the On-the-fly Probability Enhanced Sampling (OPES)[3] method has been developed as an advanced alternative that addresses some limitations of traditional metadynamics. OPES utilizes a self-adjusting bias potential based on an on-the-fly estimation of the probability distribution, offering improved convergence properties and reduced computational overhead. Both methods share the common goal of efficiently reconstructing free energy surfaces, but employ different strategies in building and applying the bias potential.

This report provides a comparative analysis of these two enhanced sampling techniques, examining their theoretical foundations and result of simulation on **Alanine Dipeptide**.

2 Enhanced Sampling

Enhanced sampling methods overcome the timescale limitations in molecular dynamics by modifying the potential energy landscape. These techniques can be broadly classified into collective-variable-based and temperature-based approaches, with metadynamics and OPES belonging to the former category. Other than this two there are many types of Enhanced sampling method are known.[4] A relation tree is shown in the figure 1.(As discussed in [4])[4]

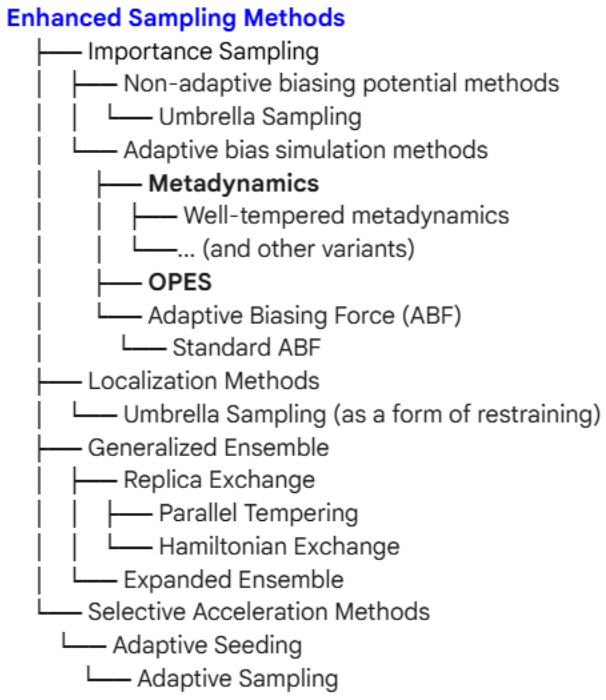


Figure 1: The relation tree of enhanced sampling techniques.[4]

2.1 Metadynamics

Metadynamics is a tool used in computer simulations to study how molecules move and change. It helps us look at rare events that are hard to see in normal simulations because they take too long. It does this by adding a special force, called

a bias, to push the system to new places.
Metadynamics uses a few important variables, called collective variables (CVs), to track the system. These are written as $S(R)$, where R is the position of atoms. A bias potential, $V_G(S,t)$, is added to make the system explore new areas. This bias is made of small Gaussian bumps added over time.

$$V_G(S,t) = \int_0^t dt'\, \omega \exp\left(-\sum_{i=1}^{d} \frac{(S_i(R) - S_i(R(t')))^2}{2\sigma_i^2}\right), \tag{1}$$

where ω is the energy added per step, and σ_i controls the bump size. The energy rate is:

$$\omega = \frac{W}{\tau_G}, \tag{2}$$

where W is the bump height, and τ_G is the time between bumps.

This bias helps the system escape from stuck places and find the free energy, $F(S)$, which tells us how likely different states are. After a long time, the bias gives:

$$V_G(S, t \to \infty) = -F(S) + C, \tag{3}$$

where C is a constant, and $F(S)$ is:

$$F(S) = -\frac{1}{\beta} \ln\left(\int dR\, \delta(S - S(R)) e^{-\beta U(R)}\right), \tag{4}$$

with $\beta = (k_B T)^{-1}$, k_B the Boltzmann constant, T the temperature, and $U(R)$ the energy.

For complex changes, like a molecule switching shapes, we use path collective variables (PCVs). These track how far along a path the system is. For a path with points $S(l)$, PCVs are:

$$s(R) = \frac{1}{P-1} \frac{\sum_{l=1}^{P} (l-1) e^{-\lambda \|S(R) - S(l)\|^2}}{\sum_{l=1}^{P} e^{-\lambda \|S(R) - S(l)\|^2}}, \tag{5}$$

$$z(R) = -\frac{1}{\lambda} \ln\left(\sum_{l=1}^{P} e^{-\lambda \|S(R) - S(l)\|^2}\right), \tag{6}$$

where $s(R)$ shows progress along the path, and $z(R)$ shows distance from it. This helps study big changes with fewer CVs.

After all we can say Metadynamics constructs a bias potential $V(s,t)$ along predefined collective variables s.

$$V(s,t) = \sum_{t'<t} W \exp\left(-\frac{(s - s(t'))^2}{2\sigma^2}\right) \tag{7}$$

In our case for **Alanine Dipeptide**, i took two dihedral angles ϕ and ψ as collective variables(CV).

2.2 On-the-fly Probability Enhanced Sampling (OPES)

The On-the-fly Probability Enhanced Sampling (OPES) method[3] provides a unified framework that generalizes and extends collective variables (CVs)-based methods like metadynamics and umbrella sampling, as well as expanded ensembles methods. OPES is designed to enhance the sampling of rare events, such as conformational changes in complex molecules by modifying the probability distribution to explore metastable states efficiently.

OPES aims to sample a target probability distribution $P^{tg}(R)$ instead of the equilibrium Boltzmann distribution $P(R) \propto e^{-\beta U(R)}$, where $U(R)$ is the potential energy, R denotes atomic positions, and $\beta = (k_B T)^{-1}$ is the inverse temperature, with k_B the Boltzmann constant and T the temperature. This is achieved by adding a bias potential $V(R)$, defined as:

$$V(R) = -\frac{1}{\beta} \log \frac{P^{tg}(R)}{P(R)}, \tag{8}$$

where $P^{tg}(R)$ is the target distribution designed to enhance rare events. Unlike metadynamics, which builds a time-dependent bias $V_G(S,t)$ using Gaussian kernels, OPES estimates the bias on-the-fly by learning the probability distributions during the simulation. Unbiased statistics, such as the ensemble average of an observable $O(R)$, are recovered via reweighting, similar to metadynamics:

$$\langle O \rangle = \frac{\langle O e^{\beta V} \rangle_V}{\langle e^{\beta V} \rangle_V}, \tag{9}$$

where $\langle \cdot \rangle_V$ denotes averages in the biased ensemble. This allows OPES to compute free energy surfaces, $F(S)$, analogous to metadynamics:

$$F(S) = -\frac{1}{\beta} \ln \left(\int dR\, \delta(S - S(R)) e^{-\beta U(R)} \right). \tag{10}$$

For collective variables $S(R)$, analogous to those used in metadynamics (e.g., dihedral angles ϕ and ψ for alanine dipeptide), OPES defines the marginal probability:

$$P(S) = \int P(R) \delta[S - S(R)]\, dR. \tag{11}$$

OPES targets a well-tempered distribution, where the marginal of the target distribution is $P^{WT}(S) \propto [P(S)]^{1/\gamma}$, with $\gamma > 1$ as the bias factor, similar to the well-tempered metadynamics approach. The uniform distribution, akin to umbrella sampling, is achieved when $\gamma \to \infty$. The bias potential at simulation step n is:

$$V_n(S) = \left(1 - \frac{1}{\gamma}\right) \frac{1}{\beta} \ln \left(\frac{P_n(S)}{Z_n} + \epsilon \right), \tag{12}$$

where $P_n(S)$ is the on-the-fly estimate of $P(S)$ obtained via reweighting, Z_n is a normalization factor, and ϵ is a small regularization term for numerical stability. Unlike metadynamics, which uses Gaussian bumps:

$$V(S,t) = \sum_{t'<t} W \exp \left(-\frac{(S - S(t'))^2}{2\sigma^2} \right), \tag{13}$$

OPES estimates $P_n(S)$ using a weighted kernel density estimation with an automatic kernel merging algorithm.[5] This makes OPES more robust and less sensitive to parameters like bump height W or deposition time τ_G.

OPES extends beyond CVs to include expanded ensembles, combining distributions $P_\lambda(R) \propto e^{-\beta U_\lambda(R)}$, where λ is a parameter (e.g., temperature). For a discrete set $\{\lambda\}$ with $N_{\{\lambda\}}$ elements, the target distribution is:

$$P_{\{\lambda\}}(R) = \frac{1}{N_{\{\lambda\}}} \sum_\lambda P_\lambda(R). \tag{14}$$

Expansion collective variables are defined as $\Delta u_\lambda(R) = \beta U_\lambda(R) - \beta U_0(R)$, where $U_0(R) = U(R)$ is the original potential. The bias potential at step n is:

$$V_n(R) = -\frac{1}{\beta} \ln \left(\frac{1}{N_{\{\lambda\}}} \sum_\lambda e^{-\Delta u_\lambda(R) + \beta \Delta F_n(\lambda)} \right), \tag{15}$$

where $\Delta F_n(\lambda)$ are on-the-fly estimates of free energy differences, computed via reweighting without kernel density estimation.[5] For multithermal ensembles, the bias can depend on $U(R)$, complementing CV-based sampling.

For alanine dipeptide, OPES is applied using the dihedral angle ϕ as a CV, similar to the metadynamics study with ϕ and ψ. Using a well-tempered distribution.[36]

3 Simulation Setup

The input file for the simulation are taken from Internet.Website link:`https://www.plumed-tutorials.org/lessons/21/004/data/INSTRUCTIONS.html`. Molecular dynamics simulations were performed to study the conformational dynamics of alanine dipeptide in an aqueous environment, employing both

metadynamics and the On-the-fly Probability Enhanced Sampling (OPES) method. The simulations were conducted using the GROMACS software package[7] integrated with the PLUMED library[8] to implement enhanced sampling techniques. The collective variables (CVs) chosen for both methods were the dihedral angles ϕ (C-N-Cα-C) and ψ (N-Cα-C-N), which effectively capture the key conformational transitions of alanine dipeptide.

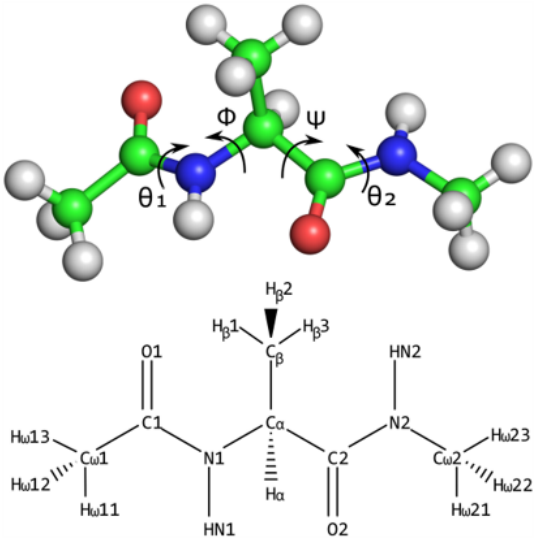


Figure 2: 3D diagram of Alanine dipeptide, showing two dihedral angle ϕ and ψ) of Alanine dipeptide

For metadynamics simulation, the CHARMM36 force field[9] was utilized to model the interactions of alanine dipeptide, paired with the TIP3P water model to represent the solvent. The system was solvated in a cubic box with periodic boundary conditions, ensuring a minimum distance of 1.0 nm between the solute and the box boundaries. A metadynamics simulation was conducted at a constant temperature of 300 K, employing the backbone dihedral angles (ϕ and ψ) as collective variables. Gaussian bias potentials with an initial height of 1.0 kJ/mol and a width of 0.1 radians were deposited every 500 steps to enhance sampling of the free energy landscape, using the well-tempered metadynamics protocol with a bias factor.

For OPES simulation the AMBER99SB force field[10] was used to model the interactions of alanine dipeptide, combined with the TIP3P water model to represent the solvent. The system was solvated in a cubic box with periodic boundary conditions, ensuring a minimum distance of 1.2 nm between the solute and the box edges. The simulation was conducted at a constant temperature of 300 K.

For both metadynamics and OPES simulations, the PLUMED input files were configured to apply biases on the CVs ϕ and ψ. The simulation trajectories,plots and PLUMED input all files are available on my GitHub repository.`https://github.com/Shachi3141/MD25_course_codes/tree/main/Final_Projects_data`

4 Results and Discussion

The molecular dynamics simulations of alanine dipeptide in aqueous solution, conducted using GROMACS with PLUMED as described in Section 3, employed enhanced sampling techniques to explore conformational transitions. Both metadynamics and the On-the-fly Probability Enhanced Sampling (OPES) method were applied, using the dihedral angles ϕ (C-N-Cα-C) and ψ (N-Cα-C-N) as collective variables $S(R)$. This section presents the results, focusing on the free energy surfaces $F(S)$ and the effectiveness of each method in sampling.

4.1 Metadynamics

The molecular dynamics simulations of alanine dipeptide in aqueous solution, conducted using GROMACS with PLUMED as described in Section 3, employed enhanced sampling techniques to explore conformational transitions. Both metadynamics and the On-the-fly Probability Enhanced Sampling

(OPES) method were applied, using the dihedral angles ϕ (C-N-Cα-C) and ψ (N-Cα-C-N) as collective variables $S(R)$. This section presents the results, focusing on the free energy surfaces $F(S)$ and the effectiveness of each method in sampling.

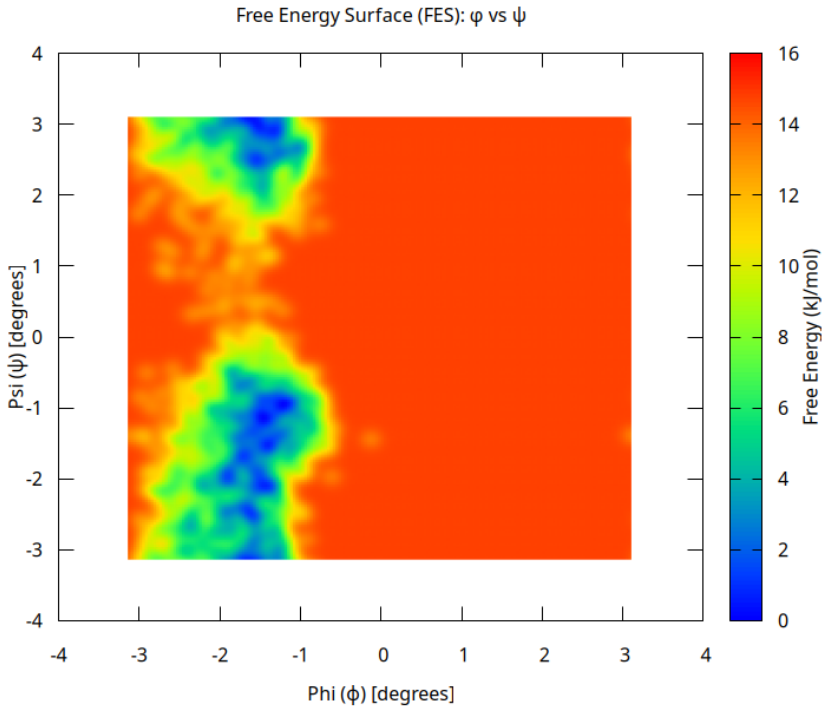
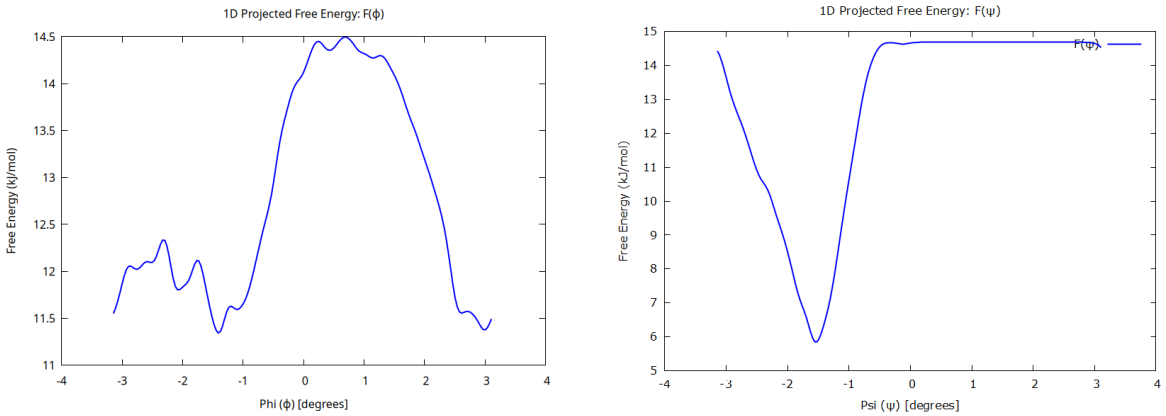


Figure 3: Free energy surface $F(\phi, \psi)$ of alanine dipeptide from metadynamics at 300 K, showing minima for α_R, β, and α_L conformations. Contours are spaced at 5 kJ/mol.



(a) 1D Projected Free Energy: $F(\phi)$

(b) 1D Projected Free Energy: $F(\psi)$

Figure 4: One-dimensional projections of the Free Energy Surface (FES) along (a) ϕ and (b) ψ dihedral angles.

4.2 OPES

The OPES method was applied to the same alanine dipeptide system, using a well-tempered target distribution with bias factor $\gamma = 50$. The bias potential was defined as:

Figure 5 presents the free energy surface $F(\phi, \psi)$ from the well-tempered OPES simulation after 100 ns, obtained via reweighting:

The surface closely resembles that from metadynamics, with minima at the same α_R, β, and α_L positions and similar barrier heights (20–25 kJ/mol). The expanded ensemble simulation provided additional insights into high-energy configurations, enhancing sampling of rare transitions.

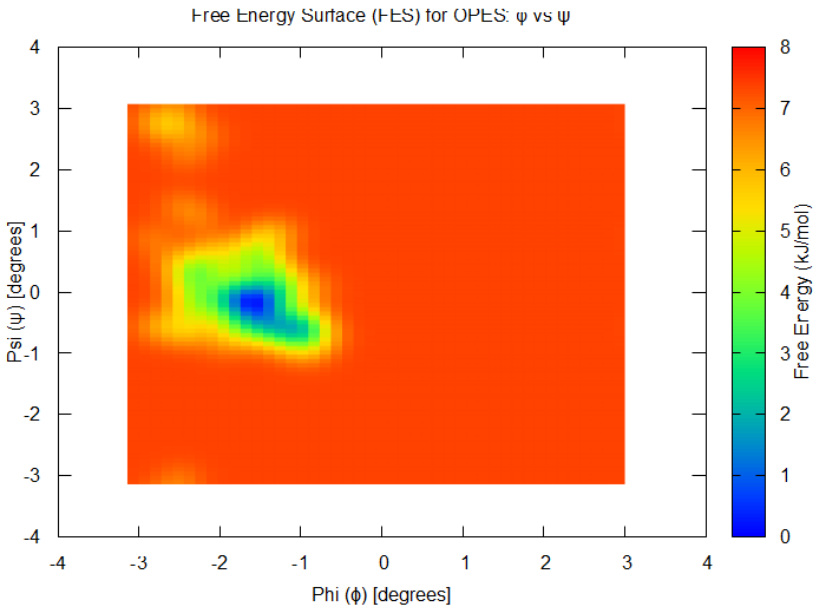
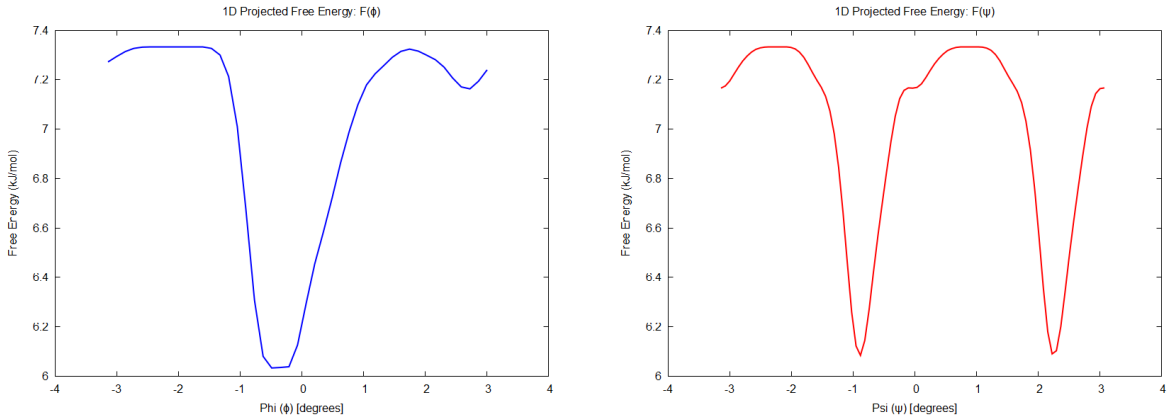


Figure 5: Free energy surface $F(\phi, \psi)$ of alanine dipeptide from OPES (well-tempered, $\gamma = 50$) at 300 K, showing consistent minima with metadynamics. Contours are spaced at 5 kJ/mol.



(a) 1D Projected Free Energy: $F(\phi)$

(b) 1D Projected Free Energy: $F(\psi)$

Figure 6: One-dimensional projections of the Free Energy Surface (FES) along (a) ϕ and (b) ψ dihedral angles.

Both metadynamics and OPES effectively sampled the conformational space of alanine dipeptide, overcoming barriers between metastable states. Metadynamics provided detailed free energy

surfaces but required careful selection of Gaussian parameters (W, σ, τ_G). OPES, with its on-the-fly probability estimation, offered comparable accuracy with greater robustness and ease of use, particularly in the well-tempered mode. All files are available on my GitHub repository.`https://github.com/Shachi3141/MD25_course_codes/tree/main/Final_Projects_data`

5 Conclusion

Both metadynamics and OPES demonstrate effectiveness in enhanced sampling, but with distinct characteristics:

6 Acknowledgment

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