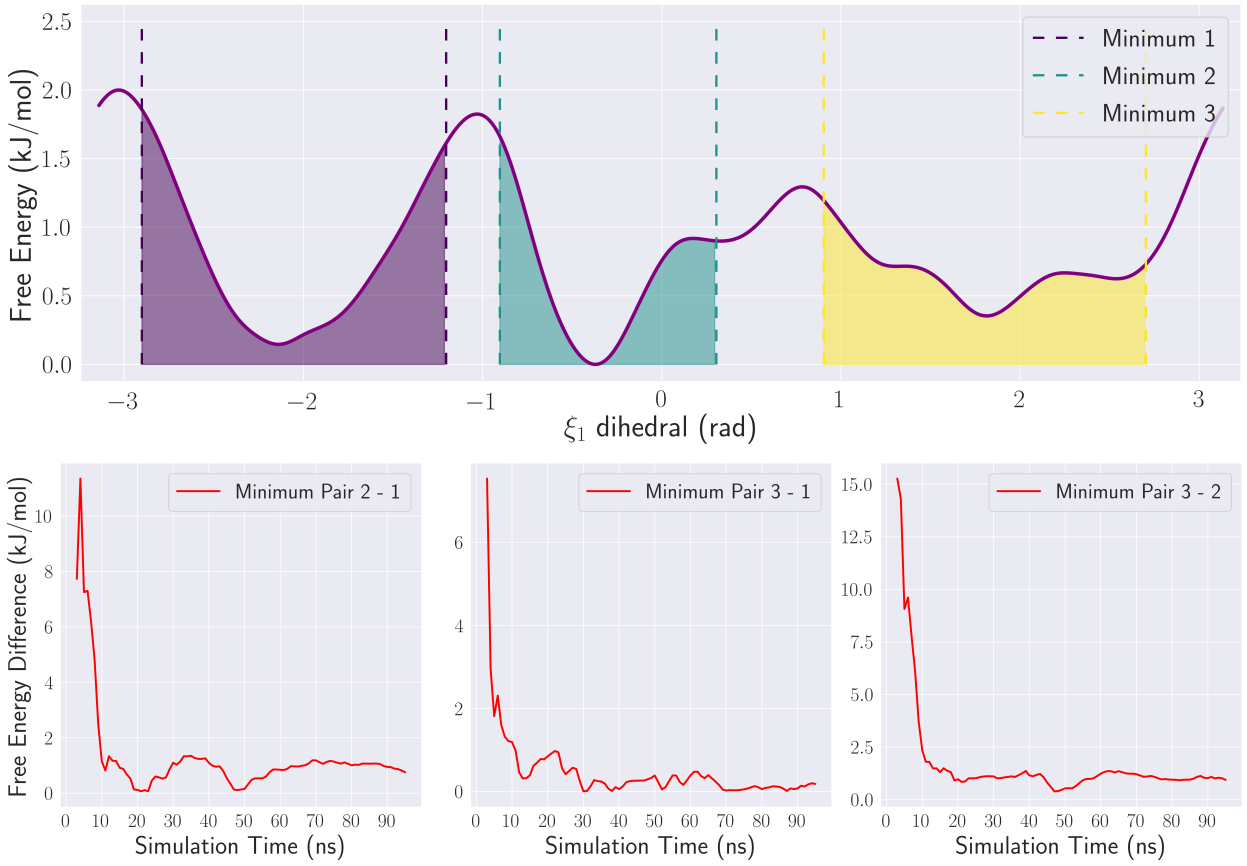
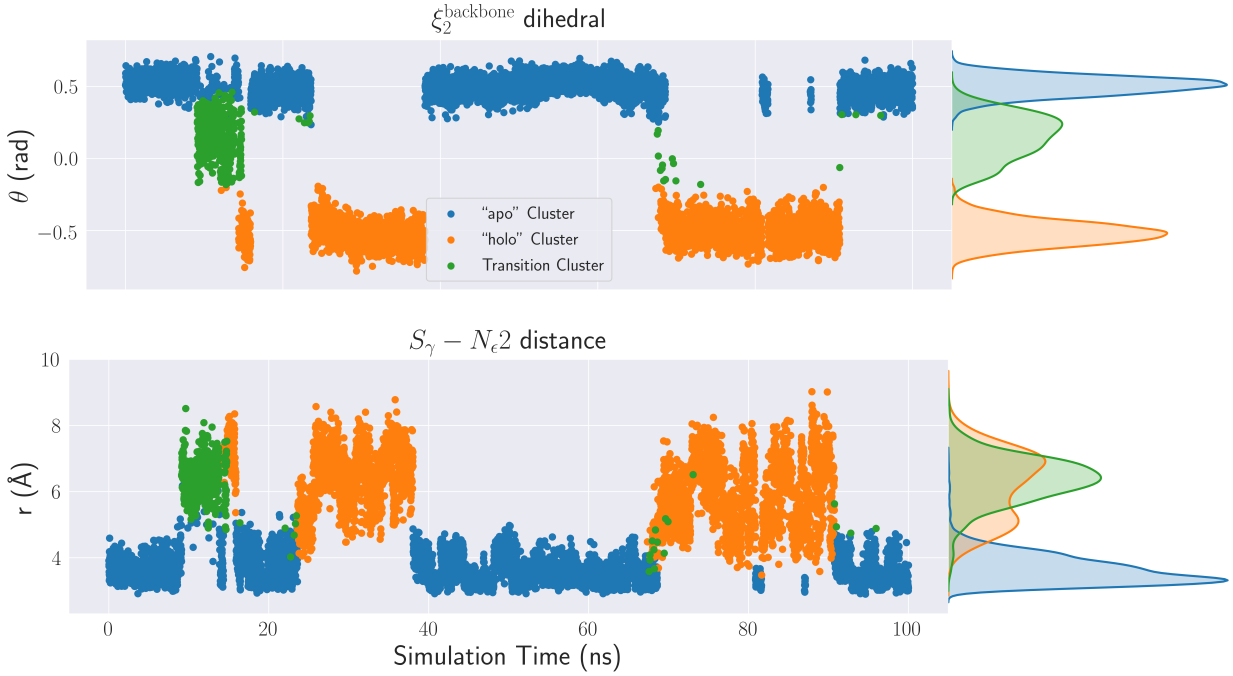
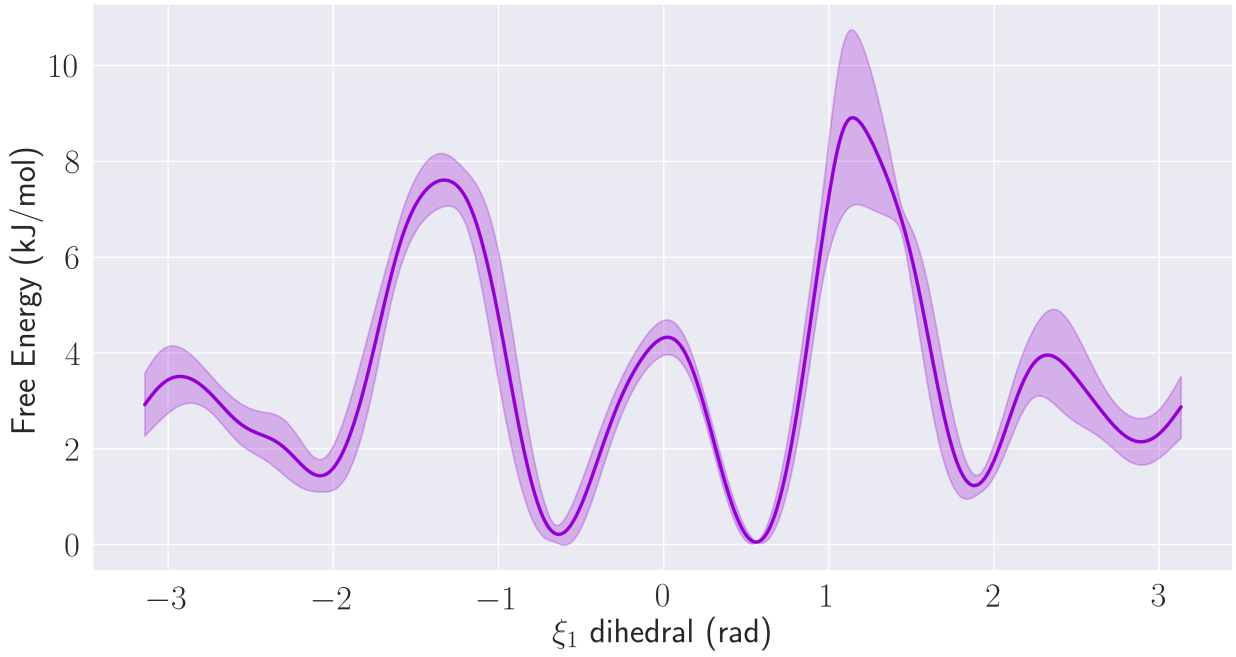
Supplementary Figures



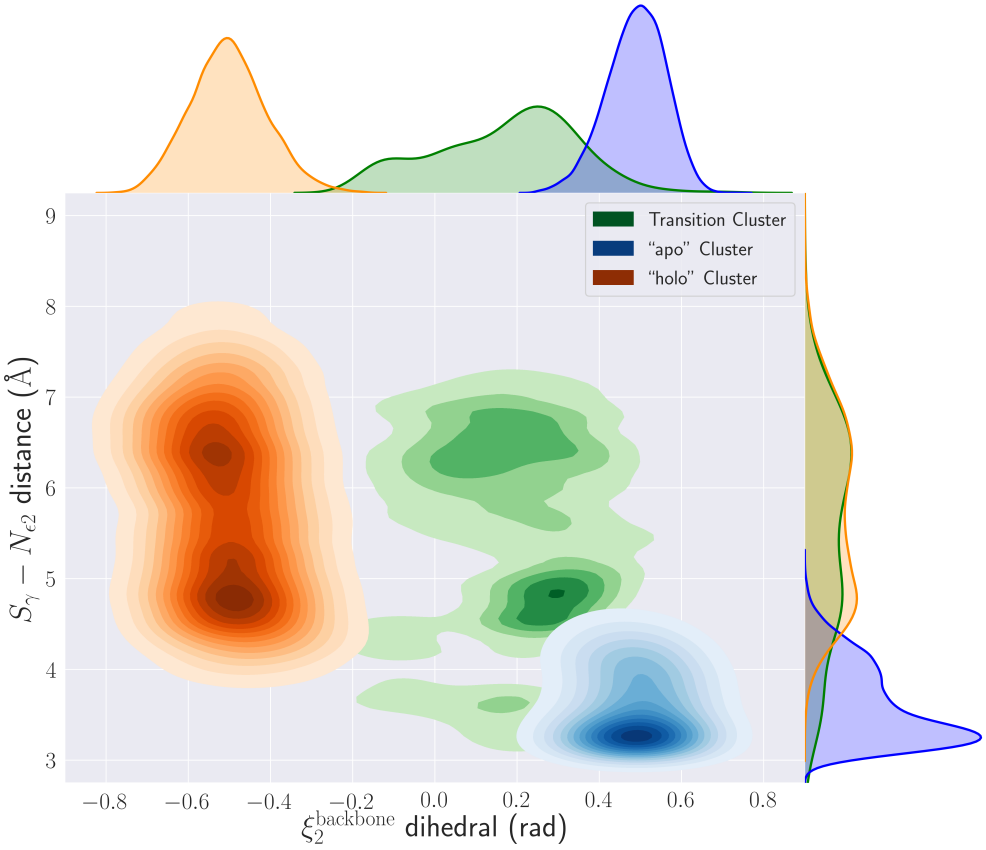
Supplementary Figure 1: Analysis of convergence of His41 imidazole dihedral MetaD bias potential. Potential of mean force (PMF) projected on the ξ_1 dihedral space of the bias potential. Relative free energy differences (in kJ/mol) were calculated between minima indicated by the dashed lines (top). Relative free energy difference between each pair of minima defined within the above PMF over the simulation time (bottom).



Supplementary Figure 2: Time evolution of the MetaD simulation trajectory and the associated cluster identity of points with respect to the His41 ξ_2^{backbone} dihedral (top) and the (Cys145-S_γ)-(His41-Nϵ) distance (bottom).



Supplementary Figure 3: Mean free energy surface obtained over 4 replicas of His41 torsional metadynamics defined within the ξ_1 dihedral space. The shaded region corresponds to the standard deviation about each free energy point calculated over the set of replicas.



Supplementary Figure 4: Probability density profiles of clusters from the aggregate trajectory of four MetaD replicas projected into the 2D CV space comprised of the His41 ξ_2^{backbone} dihedral and the (Cys145-S_γ)-(His41-Nϵ) distance. Population densities with respect to each CV axis are aligned for each cluster.

Supplementary Note 1: Clustering reproducibility

The analysis of the sampled space performed previously was repeated for the aggregate data set — the sampled points were projected into the $\xi_2^{\mathrm{backbone}}$ dihedral — (Cys145-S_γ)-(His41-Nϵ) distance CV space and were clustered into 3 distinct regions identified using Gaussian mixture modelling,[1] These regions correspond to the "apo", intermediary and "holo" states (Supplementary Fig. 4). This illustrates that in addition to the replicas reproducing the free energy surface, they too reproduce the locations of clusters from the single replica MetaD PDFs (Fig. 5).

Supplementary References

1. Pedregosa, F. *et al.* Scikit-learn: Machine learning in Python. *Journal of Machine Learning Research* **12**, 2825–2830 (2011).