Enhanced Sampling Aided Reaction Discovery

Discovering and characterizing new molecules and chemical pathways is one of the main goals of chemistry. The recent advent of artificial intelligence and machine learning is drastically changing the way chemists approach the exploration of the chemical space. While the past was mainly dominated by heuristics and specialist chemical knowledge, the future will be monopolized by automated workflows for reaction discovery and refinement of the discovered paths.[1]

Here, we exploit recent progresses in enhanced sampling methods, and propose a modular workflow for blind reaction discovery and determination of reaction paths.[2] In a three-step strategy, at first we use a collective variable derived from spectral graph theory in conjunction with the explore variant of the on-the-fly probability enhanced sampling method[3] to drive reaction discovery runs. Once different chemical products are determined, we construct an ad-hoc neural network-based collective variable to improve sampling, and finally we refine the results using the free energy perturbation theory and a more accurate Hamiltonian. We apply this strategy to challenging reactions occurring both in gas phase and complex environment.[4]

Our workflow requires minimal user input and extends the power of ab initio molecular dynamics to explore and characterize the reaction space.

References

1. Wang, L.-P.; Titov, A.; McGibbon, R.; Liu, F.; Pande, V. S.; Martínez, T. J., Discovering chemistry with an ab initio nanoreactor. *Nature Chemistry* **2014,** *6* (12), 1044-1048.
2. Raucci, U.; Rizzi, V.; Parrinello, M., Discover, Sample, and Refine: Exploring Chemistry with Enhanced Sampling Techniques. *The Journal of Physical Chemistry Letters* **2022,** *13* (6), 1424-1430.
3. Invernizzi, M.; Parrinello, M., Exploration vs Convergence Speed in Adaptive-Bias Enhanced Sampling. *Journal of Chemical Theory and Computation* **2022,** *18* (6), 3988-3996.
4. Raucci, U.; Sanchez, D. M.; Martínez, T. J.; Parrinello, M., Enhanced Sampling Aided Design of Molecular Photoswitches, *ChemRxiv* **2022**