Contribution ID: **33** Type: **Oral contribution**

Everything everywhere all at once in enhanced sampling of rare events

Thursday 10 July 2025 11:05 (30 minutes)

Most natural processes, due to the large free energy barriers that separate the metastable states, are rare events for computer simulations, making their study challenging.
To alleviate this issue, a number of enhanced sampling methods have been proposed.
Methods such as Metadynamics or On-the-fly Probability Enhanced Sampling (OPES)[1,2] aim at removing the effect of barriers to promote transitions between states by *filling* the energetic basins. This way, at convergence, the sampling of the phase space can be improved and free energy estimates recovered.
However, such methods require the definition of collective variables that encode the relevant mode of the process, which are not always easy to obtain.
In addition, such simulations hardly sample the crucial transition state (TS) region, which provides precious insights into the workings of the reactive process.
Indeed, the TS is located on saddle points of the energetic landscape, making its sampling highly unfavourable also in the biased scenario.

Recently, we proposed an approach, based on machine learning the committor function through an iterative and self-consistent procedure, to extensively sample and analyze the TS.[3]
Such a method is based on a bias potential, functional of the committor, that helps stabilize the TS region, thus favoring its sampling.

We have then greatly improved this procedure by combining it with a metadynamics-like (OPES[1,2]) enhanced sampling approach, using a logarithmic function of the committor as a collective variable.[4]
The combined action of the two biases leads to a much improved sampling in which transition and metastable states are studied with the same thoroughness, transitions are efficiently observed, and accurate free energy estimates recovered.

After the first test systems, including small proteins and host-guest systems, the method, whose code is available open-source[2], is already being applied to speed up and increase the level of detail in challenging applications in biophysics, ranging from protein dynamics driven by force-fields to enzymatic reactions at QM/MM level[5].

[1] M.Invernizzi, M. Parrinello, JPCL, 7, 2731–2736, 2020
[2] E.Trizio *et al.*, ArXiv preprint, 2024
[3] P.Kang, *E.Trizio*, M.Parrinello, Nat.Comp.Sci. 4, 451–460 2024
[4] E.Trizio, *P:Kang*, M.Parrinello, Nat.Comp.Sci. 5, — 2025
[5] S.Das *et al.*, ChemRxiv preprint, 2025

Authors: TRIZIO, Enrico (Italian Institute of Technology); Dr KANG, Peilin (Italian Institute of Technology)

Co-author: Prof. PARRINELLO, Michele (Italian Institute of Technology)

Presenter: TRIZIO, Enrico (Italian Institute of Technology)