ENHANCED SAMPLING SIMULATIONS OF BIOMOLECULAR SYSTEMS

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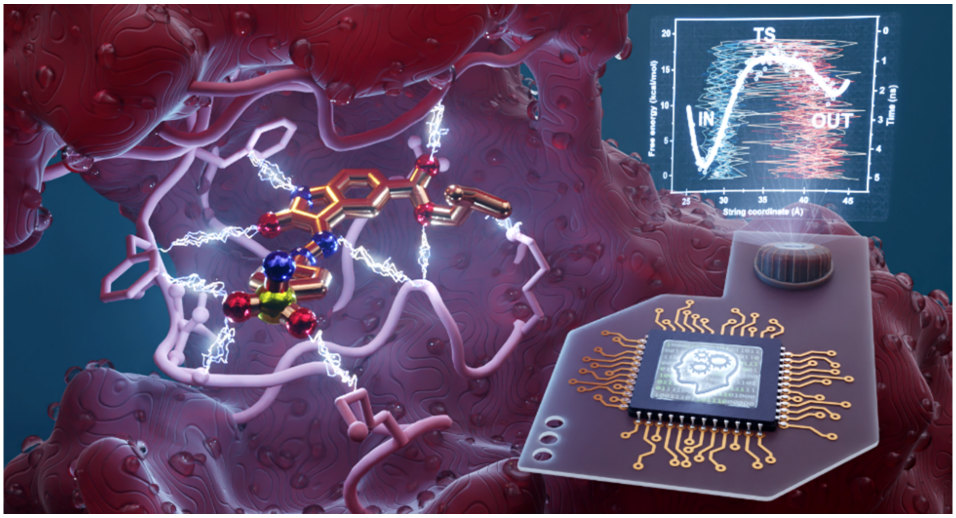
Important biological functions of biomolecular systems, such as catalysis, large-scale conformational changes, or ligand unbinding are often out of reach of atomistic molecular simulations. Enhanced sampling algorithms proved essential to mapping the pathway for these processes. However, the selection of collective variables is generally highly challenging. Here, we present algorithms [1, 2] that enable the identification of ligand unbinding pathways and pave the way for the calculation of unbinding free energy profiles. On one hand, we can determine kinetically optimal bias using mean first passage times [2] to observe biomolecular pathways. On the other hand, without *a priori* defining CVs, we can identify useful atomic distances to map the unbinding pathway [1]. Subsequently, the finite-temperature string method is used to calculate the free energy barrier and obtain an estimate of the off rate. However, the key variables that determine the transition state (TS) are not necessarily obtained. To enable the identification of the most important CVs that play a major role at the TS, we developed a general machine learning (ML) approach, applicable to any molecular processes. We generate short downhill trajectories initiated near the TS and train ML networks to predict the trajectory outcomes. These trained networks are subsequently used to pinpoint the most relevant CVs at the TSs. Our calculations are applied to drugs targeting CDK2 [1] and the M3 muscarinic acetylcholine receptor [3]. We hope to provide key molecular features that help design inhibitors based on their allosteric and kinetic properties.



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