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Bridging time-scale gaps via reaction path optimization

JHIH-WEI CHU, Department of Chemical Engineering, University of California, Berkeley

In this talk I will present a series of new computational methodologies that can be applied to systematically investigate the mechanism, free energy profiles, and rates of large-scale conformational changes of biomolecules. First, we enhance the efficiency of reaction path optimization methods, which use a series of duplicated systems, or replicas, to represent a discrete path by using holonomic constraints instead of reparametrization or using penalty potential functions that may require force projections to maintain equal distances between replicas. As a result, this formulation allows a straightforward application of super-linear optimization schemes such as the Adopted Basis Newton Raphson method, which uses much fewer energy and force evaluations to optimize a path. Novel objective functions, such as Hamiltonian and action, have also been designed for the search of novel pathways in addition to minimum energy paths. We have also generalized this approach to compute minimum free energy paths of a reaction. Second, constraints for sampling on the hyper-planes along an optimized path have been developed for computing the potential of mean force using the blue- moon approach. For obtaining rate information, we propose to solve the time-dependent Fokker-Planck equation by using the free energy profiles along a path as input. I will present the studies of two important conformational changes using these methods: the cis-to- trans isomerization of an alanine dipeptide and the helix-to-hairpin transition of an amyloid beta peptide.