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Computing Transitions in Macromolecular Systems: Dynamic Importance Sampling JUAN PERILLA, Johns Hopkins University, OLIVER BECKSTEIN, ANU NAGARAJAN, THOMAS WOOLF — Understanding and predicting conformational change in macromolecules is central to linking structure and function. Performing straight-forward all-atom molecular dynamics would, in principle, enable sampling of conformational changes. However, the time-scale for functionally important transitions, exceeds the usual MD timescales by several orders of magnitude. Thus to sample on longer time-scales requires the development of biased molecular dynamic methods, where the bias can be applied and corrected for at the end. In our approach, called 'Dynamic Importance Sampling' we generate a series of independent trajectories that are conditioned on starting and ending in defined conformations. Trajectories are generated using two different algorithms: one that uses an adaptive soft-racheting scheme, based on stochastic trajectories and, the other uses information from the set of normal modes. Both algorithms do not require a previous knowledge on the reaction coordinate, furthermore using this framework we are also able to introduce a generalized reaction coordinate in order to guide the transitions for virtually any system. The algorithms, which require no initial pathway, are capable of rapidly determining multiple pathways between known states. The associated probability scores allow us to rank order the most likely pathways.

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