Enhanced Phasespace Sampling of Biomolecular Systems Using Metastability

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One of the major problems in the simulation of molecular systems such as protein is the limitation of the simulation time. Since high frequency modes restrict the integration timestep to about 1 fs, it is not possible to reach the biological relevant timescale of several ms. This issue is often referred to as the sampling problem. Common approaches to alleviate this difficulty is to use immense amounts of computational resources or step back to coarse-grained or other simplified models.

A recent idea is to not simplify the model, but constrain the interest to some predefined system properties, which may be of thermodynamic (e.g. equilibrium constants), kinetic (e.g. transition rates), or structural type (e.g. the transition state ensemble). This allows to split the integration process into a controlled series of small simulations, which are selected in such a way that a maximum of statistical information is gathered with respect to these predefined system properties.

Our method uses an adaptive technique to construct a suitable metastable and markovian model, which reduces the complexity to a graph representation. This picture allows for a convenient and fast way to compute errors of system properties and predict initial conditions for additional simulations to collect the maximum of statistical information.

We applied the adaptive method to a small five residue peptide (MR121-GSGSW) and obtained several results indicating that the method can speed up the rate of convergence for the chosen target property, e.g. the estimated energy difference between metastable conformations, the mean first passage time or the overall number of existing metastable states in the system.

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