

The Orthogonal Space Sampling to Efficiently Calculate Free Energies

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A complex biomolecular process may involve multiple key events. To overcome existing energy barriers along the process, the first-order generalized ensemble methods, by which free energy surfaces are flattened along pre-defined order parameters, have been widely applied. Due to the fact that “hidden” energy barriers are likely to exist in the orthogonal space, “lagging” effects have been detrimental to the efficiency of free energy simulations. Facing this challenge, we have identified the generalized force as a general orthogonal space order parameter and based on this insight developed a series of the orthogonal space sampling algorithms. In this talk, besides the original orthogonal space random walk, the newly improved orthogonal space tempering and the generalized orthogonal space tempering methods will be presented. These methods allow robust and efficient calculations of free energies when little or no prior knowledge on the target system is known.