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Explorative Umbrella Sampling

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Abstract
Computer simulation can contribute significantly to our understanding of biomolecules, particularly by elucidating the free energy landscape in which they exist. A major challenge in this type of application is achieving sufficient sampling. Here we highlight a recent improved sampling method which both limits sampling to energetically relevant regions of phase space and reduces resampling of the same regions. This approach reduces the computational burden of studying complex and multidimensional free energy landscapes, extending the type and size of systems that can be simulated.

Key words: enhanced sampling; molecular dynamics, free energy, umbrella sampling, adaptive bias

One of the major contributions that computational simulations bring to the challenge of understanding the function and dynamics of biomolecular machines is in determining the relative free energy of different conformational states and the transition paths between these states. A major challenge in this type of application is to achieve sufficient sampling over all the important regions of the free energy landscape(1). Unbiased molecular dynamics spend too much time in local minima of configuration space. As a result, approaches of two general classes have been developed to enhance sampling – approaches similar to umbrella sampling(2) that are designed to evenly sample a selected subspace by constraining each simulation to a specific region and approaches similar to metadynamics(3) that adaptively add a history-dependent bias to effectively flatten the underlying free energy landscape, facilitating even sampling. Umbrella sampling reduces the computational cost by limiting the number of times a region is sampled, but requires sampling every window within a grid spanning the conformational space. The adaptive bias approaches limit the areas of phase-space that are sampled to only the most relevant regions, but resample the same regions multiple times. In both cases, either because of sampling in regions that are not physically relevant (umbrella sampling) or because of resampling the same regions (adaptive bias), the dimensionality of free-energy sampling is generally limited to 2 degrees of freedom because of computational cost.

Wojtas-Niziurski *et al* propose a hybrid free energy method designed to capture the advantages of these two classes of methods and facilitate sampling free energy landscapes of higher dimensions in their paper entitled '**Self-Learning Adaptive Umbrella Sampling Method for the Determination of Free Energy**

Landscapes in Multiple Dimensions'(4). This method starts by performing a set of umbrella sampling simulations localized around the known structures of the system of interest. After sampling, those windows with a relative energy below a user-defined energy cutoff are allowed to spawn new windows in adjacent grid regions. Umbrella sampling is performed to determine the relative energy of these new windows and the process is repeated. This method thus samples each window only once while adaptively discovering only the regions of configuration space that are relatively low in energy. The authors apply their method to three systems of increasing complexity (a model system of Lennard Jones particles, Met-enkephalin, and the KcsA potassium channel) and show that the self-learning algorithm significantly reduced the number of windows that needed to be sampled while retaining excellent agreement with the results from umbrella sampling simulations covering the entire grid in 2 dimensions. An intriguing aspect of this algorithm is that the advantage offered by limiting phase space to only low energy regions scales as the number of collective variables are increased. In the KcsA system, the authors use their method to describe the pathway by which the potassium ion traverses the channel in 3 dimensions – a problem that is not tractable with current computational resources using traditional umbrella sampling methods. The self-learning adaptive umbrella sampling technique seems an attractive method to determine free-energy landscapes that should be easy to implement with existing MD simulation software. One limitation of this method is that it cannot be parallelized to the same extent as traditional umbrella sampling since each set of umbrella sampling windows is used to guide the generation of the next set. This is not a major issue since computational cost remains more of a limiting factor in these applications than the degree of parallelization. This algorithm extends the complexity of free-energy landscapes that can be explored efficiently and thus extends the types and size of systems that are amenable to study. These types of study are important in order to couple an atomistic level understanding of the mechanisms driving biochemical processes with experimentally determined structures, rates, and transition state information for complex biophysical systems.

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