A Variational Approach to Enhanced Sampling and Free Energy Calculations

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The presence of kinetic bottlenecks severely hampers the ability of widely used sampling methods like molecular dynamics or Monte Carlo to explore complex free energy landscapes. One of the most popular methods for addressing this problem is umbrella sampling which is based on the addition of an external bias which helps overcoming the kinetic barriers. The bias potential is usually taken to be a function of a restricted number of collective variables. However constructing the bias is not simple, especially when the number of collective variables increases. Here we introduce a functional of the bias which, when minimized, allows us to recover the free energy. We demonstrate the usefulness and the flexibility of this approach on a number of examples which include the determination of a six dimensional free energy surface. Besides the practical advantages, the existence of such a variational principle allows us to look at the enhanced sampling problem from a rather convenient vantage point.