# Enhanced Sampling Methods

Markov chain Monte Carlo methods have been widely applied to otherwise intractable problems in statistical mechanics and statistical inference, such as sampling biological macromolecules on rugged energy landscapes. One key limitation of the methods, however, is that a Markov chain often becomes trapped in a local probability maximum; it does not quickly ‘mix’ across the support of the distribution. We have contributed to several simulation techniques that can improve this mixing. We showed, for the first time, that constrained dynamics can be used as one of several Monte Carlo moves that explores the entirety of configuration space in accordance with the Boltzmann distribution [1]. Subsequently, we extended the constrained dynamics software to not only perform torsional and fully flexible dynamics, but include “ball” and “cylinder joints” [2].

In addition to developing new methods, we have provided an important insight into the popular replica exchange method. We have shown that if there are a sufficient number of states in a replica exchange simulation, the precise definition of states does not affect sampling efficiency [3]. Previously, many scientists thought that the number of states in replica exchange should be carefully optimized.

Previously, David also participated in developing nonequilibrium candidate Monte Carlo, which uses a configuration obtained from a nonequilibrium driven process as a Monte Carlo trial move [4]. He also contributed to developing two other techniques that treat a probability density of interest as a sum of simpler density functions [5], [6].

## Related references

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