Enhanced Sampling Methods: Understanding the Relationship of Replica Exchange and Multicanonical Types of Methods and Predicting their Performance in Real Applications

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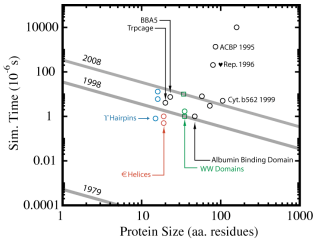
Limitations of Conventional MC and MD



Conventional Monte Carlo (MC) and Molecular Dynamics (MD) calculations have difficulty producing reliable equilibrium samples because of long relaxation times. This problem occurs in many scientific areas. For computational sampling in molecules, tremendous progress has been made over time in what can be done (**left**), but only the smallest and fastest peptides can be simulated long enough to equilibrate their conformations.

A Definition of Efficiency

We need methods that are more efficient than conventional MC and MD. Methods that are more efficient require less computational effort to estimate an equilibrium property y to some pre-determined uncertainty σ_y

$$Efficiency = \frac{1}{\sigma_y^2}\frac{1}{\text{Computational Effort}}$$

For methods in which there are N copies of the system with correlated motion, the variation of the error at long times is related to the integral of various correlation functions

$$\sigma_y^2 = \frac{C_S(0)}{N}\frac{\tau_{S,\text{int}}}{t} + \frac{N-1}{N}C_D(0)\frac{\tau_{D,\text{int}}}{t}$$
$$C_S(t) = \left\langle y_i(t_0+t)y_i(t_0)\right\rangle - \left\langle y_i\right\rangle^2$$
$$C_D(t) = \left\langle y_i(t_0+t)y_{j\neq i}(t_0)\right\rangle - \left\langle y_i\right\rangle^2$$
$$\tau_{S,\text{int}} \approx 2\int_0^\infty C_S(t)dt$$
$$\tau_{D,\text{int}} \approx 2\int_0^\infty C_D(t)dt$$

To compare the efficiencies of two methods, we can often take the computational effort to be equal to the length of the simulations times the number of copies of the system. Then the efficiency can be directly related to the integrated auto-correlation times

$$Efficiency^{-1} \approx C_S(0)\tau_{S,\text{int}} + (N-1)C_D(0)\tau_{D,\text{int}}$$

This definition forms the basis of numerical and analytic approaches for comparing enhanced sampling methods such as the replica exchange and multi-canonical methods.

Replica Exchange and Multicanonical Methods

Two popular types of methods for enhancing equilibrium sampling are replica exchange and multicanonical methods. Both methods start by adding an additional degree of freedom or dimension to the system. This additional variable is usually called λ. In the multicanonical types of methods, an additional term is added to the energy to ensure uniform sampling along the λ coordinate in some range of interest

$$U_{MUCA}(\mathbf{x}) = U(\mathbf{x};\lambda) + W(\lambda)$$

Determining the weight function W is a tedious process that often consumes the bulk of the computational effort. A number of self-consistent or iterative approaches have been suggested to determine W.

In the replica exchange methods, λ is discretized into a number of discrete (N) values λ_i. To ensure that each value of λ_i is uniformly sampled, N copies or replicas of the system are simulated in parallel. Each replica has a fixed value of λ_i. Then an additional Monte Carlo move is added to allow two replicas to exchange their values of λ_i. By allowing for exchanges, each replica is guaranteed to sample the same distribution (albeit discretized) as in the multi-canonical types of method. Although no weight function is needed to guarantee uniform sampling, multiple copies of the system must be simulated in parallel.

Important Questions for Theory

1. Which method is more efficient: multicanonical or replica methods?
2. How does this depend upon the choice of N?
3. How much more efficient are these methods than conventional MC or MD? Can we predict a-priori how efficient these methods will be?
4. How does the efficiency of these methods depend upon the choice of λ?
5. For any given λ, what is the optimal distribution of λ to sample from?

Theoretical Assumptions

1. Lambda dynamics are fast compared to structural dynamics.
2. Cross correlations between replicas are negligible in the large N limit close to equilibrium.

Theoretical Results

1. If cross-correlations are negligible, then replica exchange and multicanonical types of methods are asymptotically equivalent, i..e., they produce identical dynamical as well as equilibrium properties after equilibration and weight determination are complete.

   This assumption of negligible cross correlation has been tested on a number of simple systems **(below).** It was found that for for measuring properties at a single value of λ, cross correlations are negligible, so that multicanonical and replica types of methods are asymptotically equivalent *provided that the same λ parameter is used.*

	N	Error in $\langle x \rangle$	Error in $\langle x\delta_M \rangle$	N	Error in $\langle x \rangle$	Error in $\langle x\delta_M \rangle$
Multicanonical	**10**	**0.0394(2)**	**0.03894(4)**	**100**	**0.0316(2)**	**0.0408(6)**
Replica Exchange	**10**	**0.0139(4)**	**0.0455(10)**	**100**	**0.0104(14)**	**0.0409(4)**

For properties at different values of λ, replica methods outperform multicanonical methods by producing lower errors for the same amount of computational work.

For large N, multicanonical and replica exchange are identical for estimating values at a single value of λ.

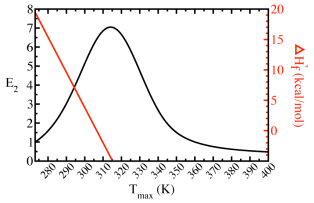
2. Because the λ variable is a fast variable, the dynamics of each replica or multicanonical simulation can be described as the motion of the system with an effective energy U_{eff}.

$$U_{eff} = -\ln\sum_{i=1}^{N}\exp\left[-U(\mathbf{x};\lambda_i)\right]$$

This allows us to predict the performance of both multicanonical and replica exchange simulations as a function of the choice of λ parameter, the limits of its variation and how it is discretized.

As an example, we can use the measured properties of the transition state for a small protein (protein L) to predict the efficiency of these methods relative to conventional molecular dynamics. Below, we show the predicted relative efficiency when λ=T is the system temperature as a function of the maximum value of λ/T.

Protein L



This shows that the efficiency of these methods is a strong function of the choice of λ and the limits over which λ is allowed to vary.

Future Work

The next step is to develop general procedures for quickly determining the optimal λ parameter for producing the most efficient multicanonical / replica exchange methods for any particular problem.

References

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H. Nymeyer (2008) How efficient is replica exchange molecular dynamics? An analytic approach. *J Chem Theory Comput* **4**(4): 626-36.