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Temperature Integration: An efficient procedure for calculation of free energy differences

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HIGHLIGHTS

- We propose an efficient method to calculate free energy differences between systems.
- The method is based on calculating for each system the $\ln Z$ difference between two temperatures.
- The calculation is performed using a Parallel Tempering procedure.
- We present a technique for equating the partition functions at high temperatures.
- We apply our method and demonstrate its efficiency on a toy model.

ARTICLE INFO

ABSTRACT

We propose a method, Temperature Integration, which allows an efficient calculation of free energy differences between two systems of interest, with the same degrees of freedom, which may have rough energy landscapes. The method is based on calculating, for each single system, the difference between the values of $\ln Z$ at two temperatures, using a Parallel Tempering procedure. If our two systems of interest have the same phase space volume, they have the same values of $\ln Z$ at high-T, and we can obtain the free energy difference between them, using the two single-system calculations described above. If the phase space volume of a system is known, our method can be used to calculate its absolute (versus relative) free energy as well. We apply our method and demonstrate its efficiency on a "toy model" of hard rods on a 1-dimensional ring.

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1. Introduction

Calculating free energy differences between two physical systems, or between two thermodynamic states of the same system, is a topic of considerable current interest. The problem arises mainly in soft condensed matter, especially in studies of macromolecules such as proteins or RNA. When the systems in question have complex energy landscapes with many local minima, generating an equilibrium ensemble of configurations in reasonable running time becomes a major challenge for computational physics. Indeed, a variety of advanced methods and algorithms have been introduced to answer the challenge, both in the context of Molecular Dynamics and Monte Carlo (for recent reviews see Refs. [1–5]).

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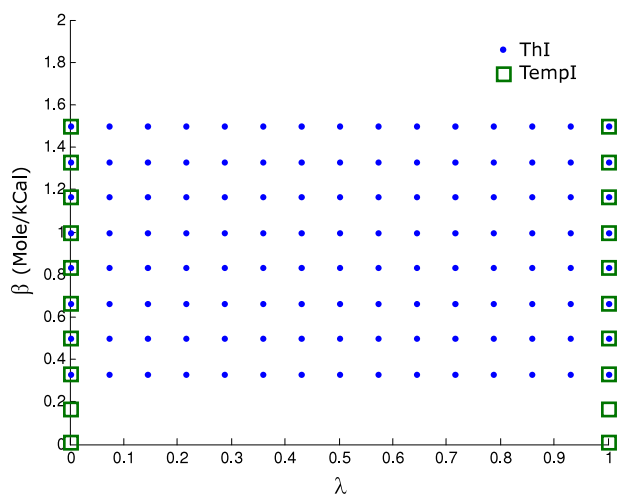
Fig. 1. Illustration of the grid of values over which the Monte-Carlo simulations are performed in the two procedures: ThI with PT and TempI. The lowest values of β correspond to some very high finite temperature.

Free energy difference between two systems can be calculated using equilibrium methods (as used by us) and non equilibrium methods. Existing equilibrium methods are composed of 3 stages: (1) selection of intermediates that interpolate between the systems (2) ergodic sampling of the system at each intermediate and (3) calculation of the free energy difference between the systems using one of the methods mentioned below. The commonly used methods include Bennett Acceptance Ratio [6], Weighted Histogram Analysis Method [7] Exponential Averaging/Free Energy Perturbation [8] and Thermodynamic Integration (ThI) [3,9,10].

Non equilibrium methods measure the work needed in the process of switching between the two Hamiltonians. These methods use Jarzynski relations [11] (fast growth is one of their variants [12]) and its subsequent generalization by Crooks [13].

Free energy differences are calculated in several contexts, including binding free energies [14–16], free energies of hydration [17], free energies of solvation [18] and of transfer of a molecule from gas to solvent [4]. Binding free energy calculations are of high importance since they can be used for molecular docking [19] and have the potential to play a role in drug discovery [20].

Most of the applications mentioned above can be tackled from a different direction using methods which measure the free energy as a function of a reaction coordinate. These methods include Adaptive Biasing Force [21] and Potential Mean Force [9].

Our novel method, Temperature Integration (TempI) can, in principle, be used instead of equilibrium methods. In order to demonstrate the advantages of TempI, we chose to introduce the idea in the context of Thermodynamic Integration (ThI) [3,9,10]. ThI is based on simulating a set of systems defined by different values of a parameter $0 \leq \lambda \leq 1$, where the two systems that we wish to compare are realized when $\lambda = 0$ or 1. The free energy difference is given as an integral over λ, which is evaluated numerically. Hence L, the number of values of λ one needs, depends on how fast the integrand varies, which in turn is determined by the dissimilarity of the two compared systems. In general, the optimal choice of the intermediate systems is a challenge [20].

Since in many cases of interest each of the systems studied has a complex energy landscape with minima separated by large barriers, equilibration times are long. A favored choice to alleviate this problem is Parallel Tempering (PT) e.g. [22] or replica exchange method [23,2] in the context of MD (Hamiltonian Replica Exchange is a variant in the λ dimension [24]). This technique necessitates equilibration of a system of N particles at a set of $n \sim \sqrt{N}$ inverse temperatures β_k, $k = 1, \ldots, n$ (where N is the number of particles).

A combination of ThI and PT has been suggested by others [25,26] as an efficient way [27] to calculate free energies of such systems. Since simulations of n replicas of the system are performed at each of L values of λ, using PT with ThI calls for simulations at a set of $L \times n$ points in the λ, T plane (see Fig. 1).

Our novel method, TempI, uses the temperature dimension, explored by Parallel Tempering, for the calculation of free energy differences; in effect the replicas, simulated in the Parallel Tempering procedure, are used as intermediates for the calculation of free energy differences. Thus, the need for sampling both T and λ dimensions is eliminated. Furthermore, since in TempI the internal energy $\langle H \rangle$ is a monotonic function of β, the choice of intermediates is no longer a challenging problem [20] (see Appendix for details), and the calculation is much easier to verify.

Temperature Integration is based on calculating, for each system, the difference between $\ln Z$ at the temperature of interest and at a high temperature, using Parallel Tempering procedures. In case the two compared systems have the same phase space and hence Z at high-T, the difference between $\ln Z$ of the systems at the temperature of interest can be calculated