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Using the method of weighted residuals to compute potentials of mean force

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Abstract

We propose a general framework for approximating the potential of mean force (PMF) along a reaction coordinate in conformational space. This framework, based on the method of weighted residuals, can be viewed as a generalization of thermodynamic integration and direct histogram methods. Using weighted residuals allows for higher-order approximations to the PMF in the form of a global spectral method or a finite element method. In addition, the higher degree of continuity provided by spectral and higher-order elements makes weighted residual methods an attractive choice for use in tandem with biasing force methods. As an analysis tool, the weighted residuals framework provides a context for direct comparison of thermodynamic integration and histogram based methods. For validation of the new method, numerical experiments are performed on two systems: a simple double-well and alanine dipeptide in vacuum. Comparisons between the new weighted residual methods, thermodynamic integration, and WHAM are performed. When configuration space is perfectly sampled the high-order weighted residual methods are found to exhibit exponential convergence. For more realistic sampling, the weighted residual methods performed comparably to the other two. However, results suggest that spectral type methods are more robust with respect to parameter choices describing the solution space.

Keywords: Potential of mean force; Method of weighted residuals; Free energy; Thermodynamic integration; Histogram methods

1. Introduction

The potential of mean force (PMF) is one of the most important concepts in physical and biological chemistry [1]. It describes the change in free energy along a "reaction coordinate" and determines the strength and likelihood of association in molecular systems [2]. Estimating the change in free energy between two molecular conformations is a challenging task due to the high dimensionality of phase space and complex structure of the energy landscape [3].

A variety of techniques have been developed to approximate the PMF including umbrella sampling [4], weighted histograms [5], free energy perturbation [6,7], thermodynamic integration [7,8], steered molecular

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dynamics [9] and adaptive biasing forces [10–13]. These methods sample configuration space using a sequence of (biased) equilibrium or nonequilibrium molecular dynamics or Monte Carlo simulations. The PMF is recovered using either the observed probability density or mean force.

In this paper we propose a novel framework for the approximation of the PMF along a reaction coordinate from configurations generated by molecular dynamics and Monte Carlo simulations. This framework, based on the method of weighted residuals, allows for the comparison of a wide class of existing free energy methods and provides a platform for deriving new methods.

Comparisons between free energy methods have been performed in the past. Both [14,15] found that thermodynamic integration (TI) was slightly superior to free energy perturbation (FEP). In a study comparing the use of the weighted histogram analysis method (WHAM), TI and FEP to compute solvation free energies, WHAM was found to perform better than TI and FEP [16]. Recently the adaptive biasing force (ABF) method was favorably compared to a method based on Jarzynski's identity [12].

The structure for the remainder of this paper is as follows. In Section 2, we define the potential of mean force in terms of the underlying probability density function. Direct histogram, thermodynamic integration and umbrella sampling methods are reviewed in Section 3. Weighted residuals methods are introduced in Section 3.4, where it is shown that direct histogram and thermodynamic integration methods are both weighted residuals methods. This framework is used to develop two new methods based on Chebyshev polynomials and spectral elements. Analytical results using a simple model problem indicate that the weighted residual methods are more accurate when conformational space is well sampled. To investigate sampling sensitivity, a sequence of numerical experiments are conducted in Section 4. Results indicate that the new weighted residual methods are competitive and more robust with respect to parameter choices.

2. Potential of mean force

The potential of mean force (PMF) is the free energy along a reaction coordinate (or path) in conformational space. The reaction coordinate, denoted by $\xi(x)$, is a function which maps atomic positions, x, to a continuous collection of states, $\xi(x)$. A specific state, ζ, is the set of atomic positions for which $\xi(x) = \zeta$. The reduced probability density function corresponding to the state ζ is given by

$$\rho_\xi(\zeta) = \int \delta(\xi(x) - \zeta)\rho(x,p)\,\mathrm{d}x\,\mathrm{d}p, \tag{1}$$

where x is the atomic positions, p is the momenta, and $\rho(x,p)$ is the probability density function associated with the ensemble. In this paper we assume conformations are sampled from the constant temperature or canonical ensemble,

$$\rho(x,p) = \frac{\mathrm{e}^{-\beta H(x,p)}}{\int \mathrm{e}^{-\beta H(x',p')}\,\mathrm{d}x'\,\mathrm{d}p'}.$$

Here $H(x,p)$ is the Hamiltonian of the system, the sum of the potential and kinetic energy terms, and $\beta = 1/k_\mathrm{B}T$, where k_B is the Boltzmann constant and T is temperature. The PMF, $A(\zeta)$, is defined in terms of the relative probability density at a state ζ by

$$A(\zeta) = -\frac{1}{\beta}\ln\left(\frac{\rho_\xi(\zeta)}{\rho_\xi(\zeta_0)}\right), \tag{2}$$

where ζ_0 is the reference state which can be chosen arbitrarily. Note that the PMF is defined up to an additive constant depending on the reference state. For a finite range of states, $[\zeta_\mathrm{a}, \zeta_\mathrm{b}]$, the reference state is often set to ζ_a in which case the resulting PMF at ζ_b is the change in free energy between states ζ_a and ζ_b.

The mean force can be written as an ensemble average using the derivative of the PMF (see [12,13]). Differentiating Eq. (2) with respect to ζ results in

$$\frac{\mathrm{d}A(\zeta)}{\mathrm{d}\zeta} = \left\langle \frac{\partial H}{\partial \zeta} \right\rangle_\zeta = -\langle F_\xi \rangle_\zeta = -\frac{\int F_\xi(x,p)\delta(\xi(x)-\zeta)\rho(x,p)\,\mathrm{d}x\,\mathrm{d}p}{\int \delta(\xi(x)-\zeta)\rho(x,p)\,\mathrm{d}x\,\mathrm{d}p}, \tag{3}$$