



A novel method for calculating relative free energy of similar molecules in two environments

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ARTICLE INFO

Article history:

Received 1 August 2016

Received in revised form 20 October 2016

Accepted 30 October 2016

Available online xxx

Keywords:

Free energy

Decoupling partition functions

Monotonicity of free energy derivative

Replica exchange

Molecular dynamics

ABSTRACT

Calculating relative free energies is a topic of substantial interest and has many applications including solvation and binding free energies, which are used in computational drug discovery. However, there remain the challenges of accuracy, simple implementation, robustness and efficiency, which prevent the calculations from being automated and limit their use. Here we present an exact and complete decoupling analysis in which the partition functions of the compared systems decompose into the partition functions of the common and different subsystems. This decoupling analysis is applicable to submolecules with coupled degrees of freedom such as the methyl group and to any potential function (including the typical dihedral potentials), enabling to remove less terms in the transformation which results in a more efficient calculation. Then we show mathematically, in the context of partition function decoupling, that the two compared systems can be simulated separately, eliminating the need to design a composite system. We demonstrate the decoupling analysis and the separate transformations in a relative free energy calculation using MD simulations for a general force field and compare to another calculation and to experimental results. We present a unified soft-core technique that ensures the monotonicity of the numerically integrated function (analytical proof) which is important for the selection of intermediates. We show mathematically that in this soft-core technique the numerically integrated function can be non-steep only when we transform the systems separately, which can simplify the numerical integration. Finally, we show that when the systems have rugged energy landscape they can be equilibrated without introducing another sampling dimension which can also enable to use the simulation results for other free energy calculations.

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1. Introduction

Calculating free energy differences between two physical systems, is a topic of substantial current interest. A variety of advanced methods and algorithms have been introduced to answer the challenge, both in the context of molecular dynamics (MD) and Monte Carlo (MC) simulations [1–7]. Applications of these methods include calculations of binding free energies [8–10], free energies of hydration [11], free energies of solvation [12], chemical reactions [13] and more. Free energy methods are extensively used by various disciplines and the interest in this field is growing—over 3500 papers using the most popular free energy computation approaches were published in the last decade, with the publication rate increasing ~17% per year [14].

Free energy difference between two systems can be calculated using equilibrium methods (alchemical free energy calculations)

and non-equilibrium methods. In equilibrium methods a hybrid system is used to transform system *A* into *B*, e.g., with the transformation

$$H_{\text{hybrid}} = \lambda H_A + (1 - \lambda) H_B, \lambda \in [0, 1], \quad (1)$$

(in practice usually more complex transformations are used as will be explained later on). In these methods, the hybrid system is simulated at a set of λ intermediates and average values are calculated. Then, using these values, the free energy difference is calculated. The commonly used methods include Exponential Averaging/Free Energy Perturbation (FEP) [15] and Thermodynamic Integration (TI) [4,16,17]. Two methods to estimate free energies which are considered equivalent are Bennett Acceptance Ratio (BAR) [18] and Weighted Histogram Analysis Method [19] (WHAM).

Another approach which enables to access directly the free energy is the Wang–Landau method, in which random walk is performed in energy space [20,21]. Other approaches such as λ Metadynamics and adiabatic MD [22,23] suggest to consider λ as a coordinate of the system and to enable the system to wander

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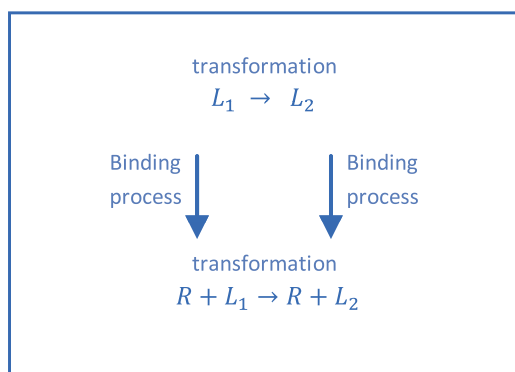


Fig. 1. The standard free energy differences scheme in the calculation of binding free energy in the existing methods.

between λ s. This is performed by introducing in the Hamiltonian a potential term which depends on λ which ensures that the system spends more time where the sampling of the free energy as a function of λ is more challenging.

In non-equilibrium methods the work needed in the process of switching between the two Hamiltonians is measured. These methods include Jarzynski relation [24] and its subsequent generalization by Crooks [25].

Calculating binding free energies is fundamental and has many applications. In particular it has potential to advance the field of drug discovery which has to cope with new challenges. In the last years the number of innovative new molecular entities for pharmaceutical purposes has remained stable at 5–6 per year. This situation is especially grim when taking into account the continual emergence of drug-resistant strains of viruses and bacteria [14]. Virtual screening methods, in which the 10^{60} possible molecules are filtered out, play a large role in modern drug discovery efforts. However, there remains the challenge of selecting the candidate molecules out of the still very large pool of molecules in reasonable times. Equilibrium methods show great potential in enabling the computation of binding free energies with reasonable computational resources. In these methods instead of simulating the binding processes directly, which would require a simulation many times the lifetime of the complex, the ligand is transmuted into another through intermediate, possibly non-physical stages. This is in fact relative free energy calculation in which the difference between free energy of a process of one molecule and another molecule is calculated. If the free energy differences between the ligands in the two environments are calculated, the relative binding free energy between the two ligands can be calculated (this cyclic calculation is called the Thermodynamic Cycle).

In Fig. 1 a scheme of the free energies in the calculation of binding free energies in the standard methods is presented (L_1 , L_2 and R represent the ligands and the receptor respectively). For solvation there is a similar scheme in which instead of a receptor there is a solvent.

Free energy calculation methods already have successes in discovering potent drugs [26]. However, despite the continuing progress in the field from the original concepts, the methods have restrictions which prevent them from being automatic and limit their use in computational drug design. A naive calculation of the free energy difference using TI can be performed as follows:

$$\begin{aligned} \Delta F_{A \rightarrow B}(\beta_1) &= \int_0^1 \frac{dF_{A \rightarrow B}(H_{\text{hybrid}}(\lambda))}{d\lambda} d\lambda \\ &= \int_0^1 \int \frac{[H_B(\Omega) - H_A(\Omega)] e^{-\beta_1[\lambda H_B(\Omega) + (1-\lambda)H_A(\Omega)]}}{Z(\lambda)} d\Omega d\lambda, \quad (2) \end{aligned}$$

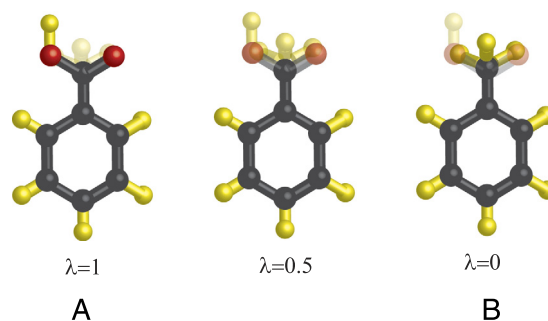


Fig. 2. A scheme of the transformation in a hybrid system in the dual topology that compares Benzoic Acid and Toluene at λ values of 0, 0.5 and 1 (one system). The transparent atoms in the end states A and B are decoupled atoms—atoms whose vdW and Coulomb interactions are removed. At $\lambda = 0.5$ the different atoms between the two subsystems are partly interacting. These calculations are often used when the compared systems have a relatively small difference (e.g., molecules that differ in few atoms). The transformation represents the top or bottom transformations in Fig. 1 where A and B represent L_1 and L_2 respectively.

where Ω denotes the vector of all coordinates. It can be seen that at $\lambda = 1$ for example H_A does not affect the systems' behavior but its energy values are averaged over, which can result in large magnitudes of the integrated function. Thus, when the systems have low phase space overlap there are significant changes in the integrated function and large variance and hence large computational cost. This is especially dominant when the two compared molecules have different covalent bond description which results in a very low phase space overlap (in the naive setup). Moreover, since molecular force fields include electrostatic and vdW terms that diverge at small atom–atom distances, the average energy can diverge at $\lambda \rightarrow 0, 1$.

A variety of approaches and techniques have been introduced to address the challenges in the field. These include the *topologies* for simulating the system, that usually take into account the fact that the compared systems have similarities to generate a hybrid system with higher phase space overlap (see Fig. 2). The topologies are usually combined with removing vdW and Coulomb terms of the different atoms which is called *decoupling* in order to further enhance phase space overlap (see e.g., Fig. 2). *Soft-core* potentials were suggested to avoid singularities at small λ s. Common sampling techniques to overcome high energy barriers include Temperature and *Hamiltonian Replica Exchange* methods [27–29]. We will explain these methodologies in the course of the derivation of the method.

However, the calculations in the existing practices have several limitations. First, they are notoriously difficult to implement correctly [30]. Such complications arise for example from the fact that the hybrid system is composed of both systems and hence it usually has to be designed (see for example dual topology in Fig. 2 and Ref. [31]). Moreover, the interactions between atoms from the two compared systems have to be ignored in order for the calculations to be reasonable. Second, since the process of transforming one system into the other is different for each comparison and has no a priori known properties, the choice of intermediates remains a challenge. In the context of TI this is equivalent to a function that needs to be numerically integrated without any known properties. In addition, since both systems interact simultaneously with the environment the behavior of the intermediate systems cannot be predicted. Third, each type of hybrid topology has small phase space overlap in one aspect [31]. Fourth, the existing decoupling analysis, while explaining several important principles, involves approximations and does not treat all the potentials [32] (such as non-quadratic terms, methyl group etc.). Fifth, the soft-core technique, while being efficient in removing singularities from the

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