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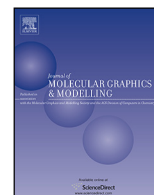

Entropy in bimolecular simulations: A comprehensive review of atomic fluctuations-based methods

Summer Kassem [a], Marawan Ahmed [b], Salah El-Sheikh [a], Khaled H. Barakat [b,c,d,*]

[a] Department of Physics, American University in Cairo, Cairo, Egypt
[b] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada
[c] Li Ka Shing Institute of Virology, University of Alberta, Edmonton, AB, Canada
[d] Li Ka Shing Applied Virology Institute, University of Alberta, Edmonton, AB, Canada

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ABSTRACT

Entropy of binding constitutes a major, and in many cases a detrimental, component of the binding affinity in biomolecular interactions. While the enthalpic part of the binding free energy is easier to calculate, estimating the entropy of binding is further more complicated. A precise evaluation of entropy requires a comprehensive exploration of the complete phase space of the interacting entities. As this task is extremely hard to accomplish in the context of conventional molecular simulations, calculating entropy has involved many approximations. Most of these golden standard methods focused on developing a reliable estimation of the conformational part of the entropy. Here, we review these methods with a particular emphasis on the different techniques that extract entropy from atomic fluctuations. The theoretical formalisms behind each method is explained highlighting its strengths as well as its limitations, followed by a description of a number of case studies for each method. We hope that this brief, yet comprehensive, review provides a useful tool to understand these methods and realize the practical issues that may arise in such calculations.

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1. Introduction

A central problem in modern drug design campaigns is the accurate and rapid determination of binding affinities [1–3]. A drug usually binds to a specific location within the target (a binding site). To be biologically active, it must physically fit within the binding site. A century ago, Fischer described this event as a lock-and-key fit. To accurately simulate this molecular recognition process, many factors must be considered, including the flexibility of the drug and its target, solvent effects, entropy contributions and the protonation states of the two molecules. While most of these factors has attracted tremendous attention throughout the last few decades [4], which led to outstanding success in their predictions, entropy still seems to be the main hurdle to calculate [5]. This is mainly due to the huge conformational space that needs to be explored during entropy calculation. This conformational flare-up results in a massively rugged potential energy surface, which involves a large number of local wells or microstates. In this context, the Gibbs free energy (G) plays a significant role in predicting the correct and physiologically relevant conformations and the differences in free energies (ΔG) determine the relative populations of these microstate [6]. For example, the free energy difference between a bound and non-bound state defines the absolute binding affinity for a given ligand.

Gibb's free energy is a sum of two different terms, namely, the change in enthalpy, ΔH, and change in entropy, $T\Delta S$, that is ($\Delta G = \Delta H - T\Delta S$), where $T$is the absolute temperature [7]. A biological process can be driven by either an enthalpic decrease or an entropic increase. As entropy depends mainly on the fluctuations of the internal coordinates of a given molecule, it seems natural that reinforcing attractive forces (i.e. enthalpic terms) reduces the number of available degrees of freedom (i.e. entropy). Such interaction between entropy and enthalpy has been observed, particularly for non-covalent binding reactions in both water and many organic solvents [8]. The three quantities ΔG, ΔH, and ΔS collectively represent the thermodynamic signature of a biological process. Predicting an accurate value for Gibb's free energy can provide a clear perspective on the overall direction of a given chemical reaction or biological process. A favorable interaction is normally correlated with a lower value of the Gibb's free energy. However, understanding the details behind this change is important,

* Corresponding author at: Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, AB T6G 2E1, Canada.
E-mail address: kbarakat@ualberta.ca (K.H. Barakat).

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particularly, to guide the design and modification of lead drug candidates.

Historically, calculating enthalpy-related terms in the Gibb's free energy has been always easier and less computationally demanding compared to calculating the entropic terms [9]. This is mainly due to the deterministic nature of the enthalpy, which usually depends on direct calculation of interacting energies (e.g. van der Waals and electrostatic energies). These energetic terms rely mainly on the atomic coordinates of the interacting atoms and can be determined rapidly and with high accuracy. On the other hand, entropy contribution is very hard to calculate, as it requires a comprehensive understanding of the complete phase space distribution of the different microstates associated with the interacting entities [9,10].

Avoiding entropy calculations has been a major trend in many computational biology studies due to the impractical computational demand associated with these calculations [11–16], particularly, for large biological systems and processes. These computational studies relied mainly on the concept of relative, rather than absolute binding energies. This concept is applicable in understanding the biology of similar processes that are associated with a well-defined reference points (e.g. the binding of very similar chemical structures to one receptor). However, there are many processes that require an accurate prediction of entropic contributions to the Gibb's free energy. This includes binding to very different ligands, protein folding, protein stability, and enzyme catalysis [17–24]. All these biological processes require a careful estimation of entropy and have been the focus of many seminal studies and methods. Despite the excellent theoretical foundations for these different methods (see below), they involve many approximations and in many cases their accuracy is unsatisfactory, keeping the field active for more innovative research and calling for new ideas and new methods to tackle this problem.

The entropy of binding can be decomposed into three well-defined terms. These include an intra-molecular configurational entropy component, ΔS_{conf}, solvation entropy component, ΔS_{solv} and a whole body rotational and translational entropy component, ΔS_{RT} [25,26]. An entropic component of a particular interest is associated with the loss of degrees of freedom due to the fact that the two bound molecules no longer move independently. Configurational or conformational entropy reflects the conformational change that takes place within both the ligand and protein upon their binding (i.e. the entropy of the internal degrees of freedom). The solvation entropy signifies the effects of the interacting solvent molecules. Some of these solvent molecules can be pushed out of the binding site while others are maintained to bridge interactions between the ligand and receptor. The translational-rotational entropy change is related to the loss of rotational and translational degrees of freedom of protein and ligand. Of all these three entropic contributions, the configurational entropy is the most influential for protein-ligand binding [27,28] and is the focus of this review. Here, we describe the most widely used methods that have been developed throughout the last three decades to estimate configurational entropy due to binding. A particular emphasis is given to the different techniques that extract entropy from atomic fluctuations. The theoretical formalisms behind each method is explained highlighting its strengths as well as its limitations, followed by a description of a number of case studies for each method. We hope that this brief, yet comprehensive, review provides a useful tool to understand these methods and realize the practical issues that may arise in such calculations.

2. Entropy and the partition function

Experimentally, recent years have witnessed a broad application of nuclear magnetic resonance techniques to estimate the change in configurational entropy [29,30]. Although this approach formed a valuable source of experimental data for this difficult problem, these NMR-based methods are still very limited. On one hand, they rely mainly on assumptions regarding the orientational distributions underlying observed order parameters, and are not yet able to account for more dynamical correlations. On the other hand they require labor intense efforts and highly sophisticated equipment, limiting the application of such methods to a few problems. Therefore, developing computational techniques that would complement/supplement current NMR methods is extremely warranted.

A typical biological process usually involves interacting molecules at thermodynamic equilibrium. Assuming that these interacting entities are in contact with a thermal reservoir at a temperature, T, and are maintained at constant volume, V, and at a constant number of atoms, N. Hence, a canonical ensemble can be used to represent the different microstates of the system. In the framework of structural biology, a microstate of a system represents a small region of the conformational space spanned by the bio-molecule/macromolecule. For peptides, this microstate can be the secondary structure adopted by the peptides, for example, a beta-hairpin. In this context, the canonical partition function is given by Eq. (1):

$$Q_N(V,T) = \frac{1}{N!h^{3N}} \int \mathrm{e}^{-\beta H(p,r)} \mathrm{d}^{3N}r\,\mathrm{d}^{3N}p$$

where h is plank's constant, $\mathrm{e}^{-\beta H(p,r)}$ is the probability for the different microstates as a function of momenta p and coordinates r, $\beta = \frac{1}{k_B T}$, k_B is Boltzmann's constant, and H is the Hamiltonian of the system. This partition function represents the volume occupied by the microstates in the phase space. For most practical problems in biology the potential energy U depends only on the system's coordinates and the kinetic energy is a function of momenta only. Therefore, these two parts of the overall Hamiltonian can be decoupled and the partition function Q can be separated into the product of two integrations. From an entropic perspective and as discussed above, we are more interested in the configurational entropy, which is related to the configurational integral, Z given by Eq. (2) below [31]. Where the configuration of the entire system is represented by the 3N-dimensional vector r:

$$Z = \int e^{-\beta U(r)} \mathrm{d}r \tag{2}$$

Hence the Probability Density Function (PDF) is given by:

$$p(r) = \frac{e^{-\beta U(r)}}{Z} = \frac{e^{-\beta U(r)}}{\int e^{-\beta U(r)} \mathrm{d}r} \tag{3}$$

Characterizing the PDF allows the exact determination of the configurational entropy:

$$S = -k_B \int p(r) \ln p(r) \mathrm{d}r \tag{4}$$

Calculating the exact configurational entropy is practically impossible through biomolecular simulations and requires infinitely long time to converge. This is mainly due to problems in incorporating all possible microstates in the entire phase space. In the context of binding free energy calculations, however, the difference in entropy (ΔS_{ij}) (i.e. relative entropy), in many cases, is the ultimate quantity to be calculated. This relative entropy can be calculated easily with

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