Chapter XLI
Entropy and Thermodynamics in Biomolecular Simulation

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ABSTRACT

Thermodynamics is one of the best established notions in science. Some recent work in biomolecular modeling has sacrificed its rigor in favor of trendy empirical methods. Even in cases where physics-based energy functions are used, entropy is forgotten or left "for later versions". This text gives an overview of the utility of a more rigorous treatment of thermodynamics at the molecular level in order to understand protein folding and receptor-ligand binding. An intuitive understanding of thermodynamics is conveyed: enthalpy is the quantity of energy, while entropy stands for its quality. Recent advances in entropy estimation from information theory and physical chemistry are outlined as they apply to biological thermodynamics. The different enthalpic, entropic, and kinetic driving forces behind protein folding and binding are detailed. Finally, some medical applications enabled by an understanding of the free energy folding funnel concept are outlined, such as HIV-1 protease folding inhibitors.

INTRODUCTION

Thermodynamics is not new and it's not trendy. Thermodynamics doesn't carry the glow of bioinformatics, pharmacokinetic modeling or metabolic networks. Should we care? In this chapter, I will argue for the importance of thermodynamics and entropy in the study of biomolecules.

The field of systems biology deals with the emerging dynamical behavior of complex networks. It is often possible to dispense with details and still understand the basic features of signaling and reaction networks. But this should ideally not happen at the cost of ignoring thermodynamic principles. It is the intention of this chapter to demystify the notions of thermodynamics relevant to biology and help the reader acquire an intuitive grasp on the meaning of entropy.

The enzymes present in a given cellular compartment determine which reactions are catalyzed and their kinetic rates. But they do not determine the directions of reactions or the amount of energy that is stored, transferred, or is required to synthesize a given reactant. (Alberty, 2006) This is predicted by thermodynamics as the direction of spontaneous processes, such as protein association events and the extent of biochemical reactions. Thermodynamics quantifies equilibrium, phase changes and stability using unmeasurable quantities like energy and entropy. These are coupled to experimentally measurable ones, like temperature and pressure, through mathematical relationships. This way, thermodynamics creates a self-consistent system of explanation for physicochemical transformations in micro- and macromolecular systems.

The concept of "free energy" has established itself as the main criterion to predict if, and to what extent, a process will occur in a spontaneous way. It represents the evolution of the qualitative idea of "chemical affinity", widespread until the 19th century. Free energy allows us to establish the equilibrium in chemical reactions and physicochemically driven processes such as non-covalent association. Important processes governed by non-covalent bonding are hormone binding to receptors, mRNA codon recognition on the ribosome (Almlöf, Andér, & Åqvist, 2007) and protein-protein interactions. Free energy allows us to predict the strength of such non-covalent interactions and the corresponding equilibrium constants.

A reliable calculation of equilibrium constants for elementary reactions among biochemical metabolites and kinetic rates of enzymes from first principles would be an invaluable advance for the field of systems biology. The methods presented in this review carry such potential.

The theoretical estimation of protein folding and ligand binding free energy is the subject of many excellent reviews (Chipot, Andricioaei, Hummer et al., 2007; Gilson & Zhou, 2007; Lazaridis & Karplus, 2003; Shakhnovich, 2006; van Gunsteren, Bakowies, Baron et al., 2006). This review will concentrate on conveying an intuitive understanding of entropy as it pertains to proteins at the molecular level, sacrificing generality but not compromising on rigor.

Many interesting developments are occurring in the field of high-throughput virtual screening and prediction of protein-protein interactions. In order to gain computational speed, some physical details will be inevitably lost. My point on insisting on a thermodynamic treatment of biomolecular interactions is that we shouldn't forget what generations of chemists have learned and replace it with ad-hoc formulations. Simplifications are useful and inevitable, so let us be guided by thermodynamics to propose models with solid foundations in physical chemistry. Simplified approaches to predict free energy which nevertheless retain a solid theoretical foundation have earned an important place in engineering thermodynamics of liquid mixtures (Mueller & Gubbins, 2001) and protein-protein binding (Audie & Scarlata, 2007).

AN INTUITIVE NOTION OF ENTROPY

Internal energy and enthalpy quantify energy. Entropy measures the quality of that energy; the lower its entropy, the more useful that energy is.

At first sight, the Earth seems to be kept alive by the energy arriving from the Sun. This is a superficial understanding, because in the steady state the amount of energy arriving from the Sun and the amount radiated back are the equal (ignoring for a moment the Earth's internal energy sources). If the energy stayed, the Earth would become unbearably warmer every day. As noted by (Schrödinger, 1944) in an