Preface of the "Symposium on calculating changes in free energy in computer simulations: Methods and applications"

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Preface of the "Symposium on Calculating Changes in Free Energy in Computer Simulations: Methods and Applications"

Ronen Zangi

Department of Organic Chemistry I, University of the Basque Country UPV/EHU, 20018, San Sebastian, Spain
IKERBASQUE, Basque Foundation for Science, 48011, Bilbao, Spain

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When simulating physical systems, the determination of the free (Gibbs) energies of the different states of the system is very desirable because it provides information on the stability of these states. To couple the system to some reference state, these calculations exploit the fact that the free energy depends only on the current state of the system and utilize the concept of a thermodynamic cycle. Furthermore, depending on the nature of the process studied the computations often use 'alchemical' mutations, thus, the transformation of atoms from one type into another. However, the determination of *absolute* free energies is very challenging. In these calculations, the process of decoupling the ligand from the rest of the system or annihilating it completely is simulated when it is free in solution as well as bound to the protein. As a consequence, there are problems in obtaining converged results, especially, when decoupling/annihilating the ligand bound to the protein. This arises because in the final stages of the transformation the ligand is weakly coupled to the environment and explores the entire simulation box.

Often we are not interested in the absolute value of the free energy (which by itself is relative to a standard state) but in the free energy *relative* to another state in the system. These relative free energies reflect relative stabilities of different states at equilibrium. This is relevant, for example, in determining receptor-ligand binding affinities, solubilities, adsorption coefficients of molecules to surfaces and conformational equilibria.

In order to compute a certain property of a state relative to another state in a selective way, we normally couple the two states. This is often done by modifying the Hamiltonian of the system by what is known as the coupling parameter approach. By changing the value of the coupling parameter, the system is transformed from one state to the other. Now there is a need to evaluate the change in free energy associated with this transformation. The two methods that are often used are the Thermodynamic Integration (TI)[1] and the Free Energy Perturbation (FEP)[2] techniques. Note that except of the landmark discovery by Jarzynski[3] that relates the free energy difference at equilibrium to an ensemble of non-equilibrium processes, there have not been any conceptual changes in the field (despite several advancements in their applications) since these methods have been introduced.

Nevertheless, the success of using these methods has increased rapidly in the last decade. The reason for this is that in order to obtain reliable results the simulated system should be able to sample all configurations with probabilities determined by the ensemble of interest. For biological applications, this is an obstacle because different stable conformations of biological molecules are held together by many, relatively strong, intra- and inter-molecular forces (hydrogen bonds, electrostatic interactions), which can be substituted by similar strength of interactions with the solvent. This results in a rugged free energy surface with numerous locally stable minima surrounded by large barriers. During a typical molecular dynamics simulation time, the system will likely be kinetically trapped in one of these minima.

Obviously, the rapid increase in computer power and its availability in the last few decades has contributed to partially circumvent this problem. Concurrently, there have been several methodological developments that helped exploring configuration space more efficiently. Escaping deep local minima usually involves the dissociation of several atom pairs to larger distances. This is the only physical route available because atoms cannot cross each other due to the hard-core repulsion at short distances. However, the advantage of computer simulations is their ability to employ non-physical routes to achieve physically meaningful results. An interesting concept, in which the interparticle potential at short distances is 'soft' instead of 'hard', has been formulated[4, 5]. For this soft-core interaction, the van der Waals

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potential is modified so that the infinite high energy that results from the overlap of atoms is replaced by a relatively low finite value. This modification allows for atoms to overlap and pass through each other and is commonly used in combination with TI and FEP methods[6, 7].

Another advancement is based on the idea that the system is able to escape the multiple local minima if it is characterized by high enough energy or temperature. Currently, the most efficient and attractive solution to this problem is obtained by the Replica Exchange Molecular Dynamics (REMD) algorithm[8, 9] and its various variants, especially those that attempt to exchange the configurations between replicas with different modified Hamiltonians (H-REMD)[10, 11, 12, 13, 14]. Utilizing these REMD methods to enhance the sampling of phase space during the free energy calculations is straightforward. However, in the case of H-REMD, it is also possible to define the Hamiltonians obtained from the coupling parameter used in TI as the modified Hamiltonians of the different replicas[15, 16, 17]. In regard to the FEP method, its major drawback is that the ensemble of configurations of the reference state should include that of the target state. A recent development has been proposed (termed Enveloping Distribution Sampling) in which the reference state is designed such that it contains the important parts of the phase space of both states[18].

For simulations at constant temperature and pressure, the Gibbs free energy is the most fundamental property of the system and the quest for its determination will perpetuate. In fact, in recent years there has been an increase in the number of studies using these computational methods. For this reason, it is likely to see continuation of method developments especially those that combine free energy calculations with efficient methods of sampling configuration space.

Ronen Zangi

Ronen Zangi obtained his B.Sc. degree in 1995 in chemistry from the Hebrew University of Jerusalem, Israel. He then moved to the University of Chicago to work on his Ph.D. thesis with Prof. Stuart A. Rice. There, he did theoretical and computational studies on phase transitions of colloidal suspensions in confined geometries. Later (1999), he moved to the Molecular Dynamics Group at the University of Groningen (Prof. Alan E. Mark) as a Marie Curie Postdoctoral Fellow where he was introduced to biomolecular simulations. At the same time, he extended his condensed phase interests to the behavior of water under confinements. In 2004 he moved to New York to work on his second postdoctoral research at Columbia University with Prof. Bruce J. Berne and studied the effect of electrolytes and cosolutes on the hydrophobic interactions. In 2008, he was appointed by the Basque Foundation for Science as an Ikerbasque Professor and joined the Faculty of Chemistry at the University of the Basque Country in San Sebastian, Spain. Currently, he is investigating solvent-induced interactions, secondary structure formation of peptides, and protein-DNA interactions.

REFERENCES

1. J. G. Kirkwood, *J. Chem. Phys.* **3**, 300–313 (1935).
2. R. W. Zwanzig, *J. Chem. Phys.* **22**, 1420–1426 (1954).
3. C. Jarzynski, *Phys. Rev. Lett.* **78**, 2690–2693 (1997).
4. M. Levitt, *J. Mol. Biol.* **170**, 723–764 (1983).
5. T. C. Beutler, A. E. Mark, R. C. van Schaik, P. R. Geber, and W. F. van Gunsteren, *Chem. Phys. Lett.* **222**, 529–539 (1994).
6. J. W. Pitera, and W. F. van Gunsteren, *J. Phys. Chem. B* **105**, 11264–11274 (2001).
7. A. Villa, R. Zangi, G. Pieffet, and A. E. Mark, *J. Comp. Aid. Mol. Design* **17**, 673–686 (2003).
8. R. H. Swendsen, and J.-S. Wang, *Phys. Rev. Lett.* **57**, 2607–2609 (1986).
9. Y. Sugita, and Y. Okamoto, *Chem. Phys. Lett.* **314**, 141–151 (1999).
10. Y. Sugita, A. Kitao, and Y. Okamoto, *J. Chem. Phys.* **113**, 6042–6051 (2000).
11. S. Jang, S. Shin, and Y. Pak, *Phys. Rev. Lett.* **91**, 058305 (2003).
12. P. Liu, B. Kim, R. A. Friesner, and B. J. Berne, *Proc. Natl. Acad. Sci. USA* **102**, 13749–13754 (2005).
13. R. Affentranger, I. Tavernelli, and E. E. D. Iorio, *J. Chem. Theory Comput.* **2**, 217–228 (2006).
14. S. Kannan, and M. Zacharias, *Proteins* **66**, 697–706 (2007).
15. C. J. Woods, J. W. Essex, and M. A. King, *J. Phys. Chem. B* **107**, 13703–13710 (2003).
16. J. Hritz, and C. Oostenbrink, *J. Chem. Phys.* **128**, 144121 (2008).
17. D. Steiner, C. Oostenbrink, F. Diederich, M. Zürcher, and W. F. van Gunsteren, *J. Comp. Chem.* **32**, 1801–1812 (2011).
18. C. D. Christ, and W. F. van Gunsteren, *J. Chem. Phys.* **126**, 184110 (2007).