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Editorial
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Novel Directions in Free Energy Methods and Applications

Free energy changes drive the vast majority of chemical processes in nature such as protein−ligand binding, polymer formation, and reaction pathways. Being able to reliably predict free energy changes using numerical simulations has long been extremely attractive as it would enable creating new processes, model reactions, and design materials and drugs with increased efficiency. Recent developments in new methods and algorithms combined with technological advances leading to impressive increases in computational power, have facilitated improvements in both the efficiency and accuracy of free energy calculations, making them useful for prospective applications such as the design of new molecules and modifications to chemical reactions.

THE BEGINNINGS

The foundations for estimating free energy differences were first developed by John Kirkwood in 1935,[1] who used fundamental principles of statistical mechanics and the concept of degree of evolution of a chemical reaction, suggested by De Donder in 1927,[2] to derive molecular pair distribution functions for fluid mixtures. In this seminal work, Kirkwood introduced the notion of the coupling parameter, which he used to calculate the free energy difference between two well-defined thermodynamic states.[1] This laid the groundwork of perturbation theory and thermodynamic integration (TI) methods, both of which rely upon the coupling parameter to describe chemical changes between two states. Peierls had also described in 1933 a perturbative expansion of the quantum partition function.[3] Lev Landau in 1938 outlined thermodynamic perturbation in his book, *Statistical Physics*,[4] which was later cited as a "thermodynamic perturbation theory" in the 1958 edition of the book, coauthored by Landau and Lifshitz.[5] A postdoc of Kirkwood, Robert Zwanzig, continued this work 20 years later, and in 1954 advanced the formalism of the free energy perturbation theory by performing a perturbation expansion on the partition function of simple nonpolar gases, in which the thermodynamic properties of a rigid sphere fluid were related to those of a slightly different system and to the difference in the intermolecular potentials of the two systems.[6] These expansions form the theoretical basis of the free energy perturbation (FEP) method. The FEP theory by Zwanzig relates the free energy difference between an initial (reference) and a final (target) state of a system to the average of a function of their energy difference evaluated by sampling for the initial state.[6]

As computational power became increasingly accessible, calculations of free energy differences in chemical systems in conjunction with molecular dynamics (MD) or Monte Carlo (MC) sampling began to emerge. The first application of FEP calculations to estimate the solvation free energy of organic molecules was published by Jorgensen in 1985.[7] In this study, relative free energies of hydration of methanol and ethane were predicted with high precision and small statistical uncertainty compared to the experimental result. The first computation of relative free energies of binding was the FEP/MD study by McCammon and co-workers, who predicted the binding of Cl^- and Br^- anions to the macrotricyclic receptor SC24 in water in excellent agreement with experimental data.[8] Following this, the McCammon and Kollman groups published the first retrospective applications of FEP for substrate binding to trypsin, thermolysin, and subtilisin in water.[9−11] The first prospective application of FEP in ligand−protein complexes was published by Merz and Kollman on three thermolysin inhibitors.[12] Furthermore, free energy profiles along a chosen coupling parameter were calculated as showcased in the work of Chandrasekhar et al.,[13] who investigated the S_N2 reaction of $Cl^- + CH_3Cl$, both in the gas phase and in aqueous solution by combining sampling enhancements and stratification strategies, laying the ground for the forthcoming hybrid quantum mechanical/molecular mechanical (QM/MM) calculations. In 1987, Jorgensen et al. then used FEP calculations to obtain the free energy profile for ion-pair separation in the S_N1 reaction of *t*-butyl chloride.[14] Tobias and Brooks also performed a technically similar FEP calculation in constructing the free energy profile for separating two tagged argon atoms in liquid argon.[15]

Although computationally very expensive at the time, these studies were the proof of concept that free energy calculations could be used to calculate (among others) relative pK_a values, medium-effects on conformational equilibria, host−guest binding affinities, free-energy surfaces for organic and biochemical reactions, and partitioning phenomena between different media such as water/octanol, water/membrane, and water/protein binding site. For examples and a more detailed discussion see the reviews in, e.g., refs 16−28.

SAMPLING ENHANCEMENT

To accurately determine the free energy difference between two states, one needs to explore the conformational space of the reference state such that relevant, low-energy conformations of the target state are adequately sampled. However, sampling techniques such as MD or MC sample along specific energy minima and are unable to overcome high energy barriers in reasonable computational times. To overcome these limitations, free energy methods and their applications have coevolved with sampling enhancement techniques and continue to do so today. The approaches discussed in this section are not free energy methods *per se* but they can be used together with them to obtain better converged estimates of free energy differences.

Starting in the 60s and 70s, a multitude of methods have been developed to generate effective non-Boltzmann sampling. Sampling can either be enhanced generally or along a specified pathway. One of the earliest and most widely used techniques is umbrella sampling, which Torrie and Valleau developed in 1977.[29,30] In umbrella sampling, a non-Boltzmann weighting (biasing) function is applied to the potential energy, which is removed at the end of the calculation to obtain the unbiased

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probability distribution. The biasing is usually performed along a pathway. Early applications of this technique to study conformational equilibria, e.g., studying Lennard-Jones liquids and subsequently water were published by the groups of Berne[31] and Jorgensen,[32] respectively. Other examples of path-based methods include approaches using a memory-dependent biasing potential such as local elevation,[33] conformational flooding,[34] metadynamics,[35] accelerated molecular dynamics[36,37] and its variant using Gaussian boost potentials,[38,39] and random expulsion molecular dynamics,[40] as well as the adaptive biasing force (ABF) method.[41,42] More recently, novel developments of these methods have emerged such as meta-extended ABF (meta-eABF)[43] and the use of the string method to compute binding free energies.[44] All of these approaches modify the free energy landscape to enhance transitions between different states of the system.

Another widely used technique that enhances sampling in a general manner (not along a specific path) and that can be combined with many different methods is replica exchange (RE). In RE, multiple copies of a system that differ in a single variable are simulated in parallel with configuration exchanges attempted at fixed intervals. RE was first introduced in 1997 using temperature as the variable (also known as parallel tempering).[45,46] A few years later, RE was combined with TI to improve the sampling in free energy calculations, where the copies are simulated at different values of the coupling parameter.[47]

DEVELOPMENTS IN METHODOLOGY

While FEP and TI are probably still the most widely used free energy methods owing to their relative simplicity and robustness, alternative free energy methods have been proposed over the years. Examples include λ-dynamics[48] and its multisite variant,[49] where the coupling parameter λ is treated as a dynamic variable such that it becomes in effect a conformational coordinate of the extended system. λ-dynamics can further be combined with local elevation and umbrella sampling to enhance sampling of λ.[50] A methodology that circumvents the coupling parameter altogether is enveloping distribution sampling (EDS),[51,52] where the reference state that is simulated is the sum of the Hamiltonians of the end states and can be modified to optimally sample all states. To simplify the parameter choice and enable the application to multiple states, EDS can be combined with replica exchange (RE-EDS).[53,54]

All methods mentioned so far are typically performed at equilibrium (i.e., transforming state A to state B in infinite time), but what happens when one wants to calculate free energy differences for very small systems or macroscopic properties in finite time? Here, nonequilibrium approaches can be employed (see refs 21 and 55 for a review) such as Jarzynski's fast growth method.[56,57] The Jarzynski relationship allows for state A to be transformed into state B in finite time. Steered MD was introduced by Izrailev et al.[58] in 1998 and was later coupled with the Jarzynski identity in 2003 to study reaction pathways.[59] This approach can be applied to understand the unfolding dynamics of proteins and peptides, ligand unbinding pathways, or the energetics of a ligand moving through a channel (see, e.g., refs 60 and 61).

OPPORTUNITIES FOR MACHINE LEARNING

Machine learning (ML), and more recently especially deep neural networks, have found wide application in computational chemistry. For example, the prediction of activity of a new compound is a common task in (ligand-based or structure-based) virtual screening and quantitative structure−activity relationship (QSAR) models, where the use of ML was generally found to improve the results (for reviews see, e.g., refs 62−64). Similarly, physicochemical properties such as partition coefficients can be expressed as free energy differences and thus, can either be obtained from MD-based free energy calculations or from quantitative structure−property relationship (QSPR) models.[65] Such ML approaches are purely statistical, and there is a long-standing debate (with different benchmarking studies[66,67]) around whether or not rigorous free energy calculations truly outperform simpler techniques.

Furthermore, new directions are being explored to combine MD simulations with ML to estimate free energy differences. A major application area is the use of ML to enhance sampling in MD simulations, which can also be employed in free energy calculations. Examples include learning of the optimal biasing potential given a set of input features,[68−70] learning of optimal collective variables,[71−75] learning of the free energy surface,[76] or learning of low-energy states without specifying a reaction coordinate.[77] An alternative approach to use ML in free energy calculations is to derive MD-based descriptors that can be used as input to train ML models. For example, MD fingerprints (MDFPs),[78,79] which encode property distributions extracted from MD simulations, can be used as a descriptor to train ML models on solvation free energies and partition coefficients.

Further advances in computer power and ML methods will create exciting opportunities for additional combined ML and MD approaches.

CONCLUDING REMARKS AND CALL FOR PAPERS

The development and application of free energy methods have a long history and a highly active present. Novel approaches and applications of these methods are emerging regularly. Many of the challenges in sampling, computing power, and methodology have been addressed in recent years by academic and industrial researchers, who have programmed free energy methods on graphics processing units (GPUs) and on cloud computing resources, developed force-fields in line with drug-like molecules, and automated the setup and analysis of the simulations.[27,80,81] Today, free energy calculations are used on a regular basis in industry for structure-based drug design projects, as shown by the recent influx of free energy methods (implicit and explicit solvent) within academic and commercial software packages. These approaches can furthermore be employed to understand the free-energy differences in protein folding and ligand binding associated with protein folding, rare event sampling including binding and unbinding kinetics, free energies of solids, absolute free energies of binding in ligand-host systems, and many more phenomena (see refs 16−28 and 82−84 for examples).

It is on this vein that JCIM is aiming to publish a special issue on Novel Directions in Free Energy Methods and Applications for publication in the Fall of 2020. The issue will be spearheaded by the authors of this Editorial and the submission deadline is May 1, 2020. In this special issue, we aim to illustrate the potential of free energy methods, the

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breadth of applications, and new directions including ML algorithms. We encourage the submission of research articles, application notes for novel methodology developments, as well as perspectives and letters. We hope that the free energy community will enthusiastically embrace this special issue and showcase the variety of methods available for free energy calculations as well as their utility in challenging questions in chemistry, biology, and materials science. We look forward to receiving submissions toward the exciting developments in methods and applications of free energy calculations.

Kira A. Armacost[*,†]
Sereina Riniker[*,‡]
Zoe Cournia[*,¶]

[†]Computational and Structural Chemistry, MRL, Merck & Co., Inc. West Point, Pennsylvania 19486, United States
[‡]Laboratory of Physical Chemistry, ETH Zürich, Vladimir-Prelog-Weg 2, 8093 Zürich, Switzerland
[¶]Biomedical Research Foundation Academy of Athens, Soranou Ephessiou 4, 11527 Athens, Greece

AUTHOR INFORMATION

Corresponding Authors

*E-mail: kira.armacost@merck.com (K.A.).
*E-mail: sriniker@ethz.ch (S.R.).
*E-mail: zcournia@bioacademy.gr (Z.C.).

ORCID

Kira A. Armacost: 0000-0001-9322-7981
Sereina Riniker: 0000-0003-1893-4031
Zoe Cournia: 0000-0001-9287-364X

Notes

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