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Andrew Pohorille  
*Editors*

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# Free Energy Calculations

Theory and Applications  
in Chemistry and Biology

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Ch. Chipot A. Pohorille (Eds.)

# Free Energy Calculations

Theory and Applications  
in Chemistry and Biology

With 85 Figures, 11 in Color and 2 Tables

 Springer

### Christophe Chipot

Equipe de Dynamique des Assemblages Membranaires  
UMR CNRS/UHP 7565  
Université Henri Poincaré, BP 239  
54506 Vandœuvre-lès-Nancy cedex  
France  
E-Mail: Christophe.Chipot@edam.uhp-nancy.fr

### Andrew Pohorille

University of California San Francisco  
Department of Pharmaceutical Chemistry  
600 16th Street  
San Francisco, CA 94143, USA  
and  
NASA Ames Research Center  
MS 239-4  
Moffett Field, CA 94035, USA  
E-Mail: pohorill@max.arc.nasa.gov

#### *Series Editors:*

#### Professor A.W. Castleman, Jr.

Department of Chemistry, The Pennsylvania State University  
152 Davey Laboratory, University Park, PA 16802, USA

#### Professor J.P. Toennies

Max-Planck-Institut für Strömungsforschung, Bunsenstrasse 10  
37073 Göttingen, Germany

#### Professor K. Yamanouchi

University of Tokyo, Department of Chemistry  
Hongo 7-3-1, 113-0033 Tokyo, Japan

#### Professor W. Zinth

Universität München, Institut für Medizinische Optik  
Öttingerstr. 67, 80538 München, Germany

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## Foreword

Andrew Pohorille and Christophe Chipot

In recent years, impressive advances have been made in the calculation of free energies in chemical and biological systems. Whereas some of this be ascribed to a rapid increase in computational power, progress has been facilitated primarily by the emergence of a wide variety of methods that have greatly improved both the efficiency and accuracy of free energy calculations. This progress has, however, come at a price: it is increasingly difficult for researchers to find their way through the maze of available computational techniques. Why are there so many methods? Are they conceptually related? Do they differ in efficiency and accuracy? Why do methods that appear to be very similar carry different names? Which method is the best for a specific problem? These questions leave not only most novices but also many experts in the field confused and desperately looking for guidance.

As a response, we attempt to present in this book a coherent account of the concepts that underlie the different approaches devised for the determination of free energies. Our guiding principle is that most of these approaches are rooted in a few basic ideas, which have been known for quite some time. These original ideas were contributed by such pioneers in the field as John Kirkwood [1, 2], Robert Zwanzig [3], Benjamin Widom [4], John Valleau [5] and Charles Bennett [6]. With a few exceptions, recent developments are not so much due to the discovery of ground-breaking, new fundamental principles, but rather to astute and ingenious ways of applying those already known. This statement is not meant as a slight on the researchers who have contributed to these developments. In fact, they have produced a considerable body of beautiful theoretical work, based on increasingly deep insights into statistical mechanics, numerical methods and their applications to chemistry and biology. We hope, instead, that this view will help to introduce order into the seemingly chaotic field of free energy calculations.

The present book is aimed at a relatively broad readership that includes advanced undergraduate and graduate students of chemistry, physics and engineering, post-doctoral associates and specialists from both academia and industry who carry out research in the fields that require molecular modeling and numerical simulations. This book will also be particularly useful to students in biochemistry, structural

biology, bioengineering, bioinformatics, pharmaceutical chemistry, as well as other related areas, who have an interest in molecular-level computational techniques.

To benefit fully from this book readers should be familiar with the fundamentals of statistical mechanics at the level of a solid undergraduate course, or an introductory graduate course. It is also assumed that the reader is acquainted with basic computer simulation techniques, in particular the molecular dynamics (MD) and Monte Carlo (MC) methods. Several very good books are available to learn about these methodologies, such as that of Allen and Tildesley [7], or Frenkel and Smit [8]. In the case of Chaps. 4 and 11, a basic knowledge of classical and quantum mechanics, respectively, is a prerequisite. The mathematics required is at the level typically taught to undergraduates of science and engineering, although occasionally more advanced techniques are used.

The book consists of 14 chapters, in which we attempt to summarize the current state of the art in the field. We also offer a look into the future by including descriptions of several methods that hold great promise, but are not yet widely employed. The first six chapters form the core of the book. In Chap. 1, we define the context of the book by recounting briefly the history of free energy calculations and presenting the necessary statistical mechanics background material utilized in the subsequent chapters.

The next three chapters deal with the most widely used classes of methods: free energy perturbation (FEP) [3], methods based on probability distributions and histograms, and thermodynamic integration (TI) [1, 2]. These chapters represent a mix of traditional material that has already been well covered, as well as the description of new techniques that have been developed only recently. The common thread followed here is that different methods share the same underlying principles. Chapter 5 is dedicated to a relatively new class of methods, based on calculating free energies from nonequilibrium dynamics. In Chap. 6, we discuss an important topic that has not received, so far, sufficient attention – the analysis of errors in free energy calculations, especially those based on perturbative and nonequilibrium approaches.

In the next three chapters, we cover methods that do not fall neatly into the four groups of approaches described in Chaps. 2–5, but still have similar conceptual underpinnings. Chapter 7 is devoted to path sampling techniques. They have been, so far, used primarily for chemical kinetics, but recently have become the object of increased interest in the context of free energy calculations. In Chap. 8, we discuss a variety of methods targeted at improving the sampling of phase space. Here, readers will find the description of techniques such as multi-canonical sampling, Tsallis sampling and parallel tempering or replica exchange. The main topic of Chap. 9 is the potential distribution theorem (PDT). Some readers might be surprised that this important theorem comes so late in the book, considering that it forms the theoretical basis, although often not spelled out explicitly, of many methods for free energy calculations. This is, however, not by accident. The chapter contains not only relatively well-known material, such as the particle insertion method [4], but also a generalized formulation of the potential distribution theorem followed by an outline of the quasi-chemical theory and its applications, which may be unfamiliar to many readers.

Chapters 10 and 11 cover methods that apply to systems different from those discussed so far. First, the techniques for calculating chemical potentials in the grand canonical ensemble are discussed. Even though much of this chapter is focused on phase equilibria, the reader will discover that most of the methodology introduced in Chap. 3 can be easily adapted to these systems. Next, we will provide a brief presentation of the methods devised for calculating free energies in quantum systems. Again, it will be shown that many techniques described previously for classical systems, such as PDT, FEP and TI, can be profitably applied when quantum effects are taken into account explicitly.

In Chap. 12, we discuss approximate methods for calculating free energies. These methods are of particular interest to those who are interested in computer-aided drug design and in silico genetic engineering. Chapter 13 provides a brief and necessarily incomplete review of significant, current and future applications of free energy calculations to systems of both chemical and biological interest. One objective of this chapter is to establish the connection between the quantities obtained from computer simulations and from experiments. The book closes with a short summary that includes recommendations on how the different methods presented here should be chosen for several specific classes of problems. Although the book contains no exercises, most chapters provide examples and pseudo-codes to illustrate how the different free energy methods work.

Each chapter is written by one or several authors, who are specialists in the area covered by the chapter. In spite of considerable efforts, this arrangement does not guarantee the level of consistency that could be attained if the book were written by a single or a small number of authors. The reader, however, gets something in return. By recruiting experts in different areas to write individual chapters, it is possible to achieve the depth in the treatment of each subject matter, that would otherwise be very hard to reach.

The material of this book is presented with greater rigor and at a higher level of detail than is customary in general reviews and book chapters on the same subject. We hope that theorists who are actively involved in research on free energy calculations, or want to gain depth in the field, will find it beneficial. Those who do not need this level of detail, but are simply interested in effective applications of existing methods, should not feel discouraged. Instead of following all the mathematical developments, they may wish to focus on the final formulas, their intuitive explanations, and some examples of their applications. Although the chapters are not truly self-contained, they may, nevertheless, be read individually, or in small clusters, especially by those with sufficient background knowledge in the field.

Several interesting topics have been excluded, perhaps somewhat arbitrarily, from the scope of this book. Specifically, we do not discuss analytical theories, mostly based on the integral equation formalism, even though they have contributed importantly to the field. In addition, we do not discuss coarse-grained, and, in particular, lattice and off-lattice approaches. At the opposite end of the wide spectrum of methods, we do not deal with purely quantum mechanical systems consisting of a small number of atoms.



On several occasions, the reader will notice a direct connection between the topics covered in the book and other, related areas of statistical mechanics, such as the methodology of computer simulations, nonequilibrium dynamics or chemical kinetics. This is hardly a surprise because free energy calculations are at the nexus of statistical mechanics of condensed phases.

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## References

1. Kirkwood, J. G., Statistical mechanics of fluid mixtures, *J. Chem. Phys.* **1935**, *3*, 300–313
2. Kirkwood, J. G., in *Theory of Liquids*, Alder, B. J., Ed., Gordon and Breach, New York, 1968
3. Zwanzig, R. W., High-temperature equation of state by a perturbation method. I. Non-polar gases, *J. Chem. Phys.* **1954**, *22*, 1420–1426
4. Widom, B., Some topics in the theory of fluids, *J. Chem. Phys.* **1963**, *39*, 2808–2812
5. Torrie, G. M.; Valleau, J. P., Nonphysical sampling distributions in Monte Carlo free energy estimation: umbrella sampling, *J. Comput. Phys.* **1977**, *23*, 187–199
6. Bennett, C. H., Efficient estimation of free energy differences from Monte Carlo data, *J. Comp. Phys.* **1976**, *22*, 245–268
7. Allen, M. P.; Tildesley, D. J., *Computer Simulation of Liquids*, Clarendon, Oxford, 1987
8. Frenkel, D.; Smit, B., *Understanding Molecular Simulations: From Algorithms to Applications*, Academic, San Diego, 1996

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## List of Contributors

**Ioan Andricioaei**

Department of Chemistry  
Center for Computational Medicine and  
Biology  
University of Michigan  
Ann Arbor, Michigan 48109–1055  
andricio@umich.edu

**Dilip Asthagiri**

Theoretical Division  
Los Alamos National Laboratory  
Los Alamos, New Mexico 87545  
dilipa@lanl.gov

**Thomas L. Beck**

Departments of Chemistry and Physics  
University of Cincinnati  
Cincinnati, Ohio 45221–0172  
thomas.beck@uc.edu

**Christophe Chipot**

Equipe de Dynamique des Assemblages  
Membranaires  
UMR CNRS/UHP 7565  
Université Henri Poincaré, BP 239  
54506 Vandœuvre-lès-Nancy cedex  
France  
Christophe.Chipot@edam.  
uhp-nancy.fr

**Eric Darve**

Mechanical Engineering Department  
Stanford University  
Stanford, California 94305  
darve@stanford.edu

**Christoph Dellago**

Faculty of Physics  
University of Vienna  
Boltzmannngasse 5, 1090 Vienna, Austria  
Christoph.Dellago@univie.ac.at

**Gerhard Hummer**

Laboratory of Chemical Physics  
National Institute of Diabetes and  
Digestive and Kidney Diseases  
National Institutes of Health  
Building 5, Room 132  
Bethesda, Maryland 20892–0520  
gerhard.hummer@nih.gov

**Nandou Lu**

Departments of Physiology and of  
Biophysics and Biophysical Chemistry  
School of Medicine  
Johns Hopkins University  
Baltimore, Maryland 21205  
nlu@groucho.med.jhmi.edu

XVIII List of Contributors

**Alan E. Mark**

Institute for Molecular Bioscience  
The University of Queensland  
Brisbane QLD 4072 Australia  
a.mark@uq.edu.au

**Athanasios Z. Panagiotopoulos**

Department of Chemical Engineering  
Princeton University  
Princeton, New Jersey 08544  
azp@princeton.edu

**Vijay S. Pande**

Departments of Chemistry  
and of Structural Biology  
Stanford University, Stanford  
California 94305  
pande@stanford.edu

**Andrew Pohorille**

University of California San Francisco,  
Department of Pharmaceutical  
Chemistry,  
600 16th Street,  
San Francisco, CA 94143, USA  
and  
NASA Ames Research Center  
MS 239-4  
Moffett Field, CA 94035, USA  
pohorill@max.arc.nasa.gov

**Lawrence R. Pratt**

Theoretical Division  
Los Alamos National Laboratory  
Los Alamos, New Mexico 87545  
lrp@lanl.gov

**M. Scott Shell**

Department of Pharmaceutical  
Chemistry  
University of California San Francisco  
600 16th Street, Box 2240  
San Francisco, California 94143  
shell@maxwell.ucsf.edu

**Thomas Simonson**

Laboratoire de Biochimie  
UMR CNRS 7654  
Department of Biology  
Ecole Polytechnique  
91128 Palaiseau, France  
Thomas.Simonson@polytechnique.fr

**Thomas B. Woolf**

Departments of Physiology and of  
Biophysics and Biophysical Chemistry  
School of Medicine  
Johns Hopkins University  
Baltimore, Maryland 21205  
woolf@groucho.med.jhmi.edu

## Introduction

Christophe Chipot, M. Scott Shell and Andrew Pohorille

### 1.1 Historical Backdrop

To understand fully the vast majority of chemical processes, it is often necessary to examine their underlying free energy behavior. This is the case, for instance, in protein–ligand binding and drug partitioning across the cell membrane. These processes, which are of paramount importance in the field of computer-aided, rational drug design, cannot be predicted reliably without knowledge of the associated free energy changes.

The reliable determination of free energy changes using numerical simulations based on the fundamental principles of statistical mechanics is now within reach. Developments on the methodological front in conjunction with the continuous increase in computational power have contributed to bringing free energy calculations to the level of robust and well-characterized modeling tools, while widening their field of applications.

#### 1.1.1 The Pioneers of Free Energy Calculations

The theory underlying free energy calculations and several different approximations to its rigorous formulation were developed a long time ago. Yet, due to computational limitations at the time when this methodology was introduced, numerical applications of this theory remained very limited. In many respects, John Kirkwood laid the foundations for what would become standard methods for estimating free energy differences – perturbation theory and thermodynamic integration (TI) [1, 2]. Reconciling statistical mechanics and the concept of degree of evolution of a chemical reaction, put forth by Théophile De Donder [3] in his work on chemical affinity, Kirkwood introduced in his derivation of integral equations for liquid-state theory the notion of the order parameter, or generalized extent parameter, and used it to infer the free energy difference between two well-defined thermodynamic states [1, 2].

Almost 20 years later, Robert Zwanzig [4] followed a perturbative route to free energy calculations, showing how physical properties of a hard-core molecule change upon adding a rudimentary form of an attractive potential. The high-temperature