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A critical analysis of various aspects of biomolecular simulation: from electrostatic forces, NMR spectra, and entropy to peptide folding

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presented by
CHRISTINE PETER
Dipl. Chem., Universität Freiburg i. Br. (D)
born January 18, 1974
citizen of Germany

accepted on the recommendation of
Prof. Dr. Wilfred F. van Gunsteren, examiner
Prof. Dr. Philippe Hünenberger, Prof. Dr. Alan Mark, co-examiners

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Contents

Kurzfassung

Molekulardynamiksimulationen (MD Simulationen) liefern ein atomar aufgelöstes Bild von molekularen Systemen, mit dessen Hilfe man Informationen über Struktur und Funktionsweise des betreffenden Moleküls erhalten kann.

Kapitel 1 gibt einen kurzen Überblick über Simulationstechniken, speziell in Hinblick auf Näherungen, die gemacht werden (müssen), um Simulationen von biomolekularen Systemen überhaupt erst zu ermöglichen. Ausserden werden verschiedene Aspekte des Simulationsprozesses näher beleuchtet: (*i*) die Anwendung auf biologisch relevante Systeme, (*ii*) die Verifizierung der Simulationsergebnisse durch Vergleich mit experimentellen Daten, (*iii*) die Validierung des verwendeten Modells und seinen Näherungen und (*iv*) die Entwicklung neuer Techniken.

MD Simulationen leisten einen wichtigen Beitrag zu unserem Verständis des Faltungsprozesses von Biomolekülen, speziell Proteinen. Peptide dienen hier als Modellsysteme, die klein genug sind, so dass man wiederholt den Übergang zwischen gefaltetem und ungefaltetem Zustand simulieren kann. Durch diese Studien gewinnt man Erkenntnisse über den Ablauf des Faltungsprozesses, das Aussehen des ungefalteten Zustandes und auch über die Präferenzen gewisser Sequenzen für bestimmte Strukturelemente. In Kapitel 2 wird das Faltungsverhalten eines kleinen nicht-natürlichen Peptides aus Aminoxysäuren in Abhängigkeit von Simulationsbedingungen wie Temperatur und Lösungsmittel untersucht.

Der Vergleich von Simulationsergebnissen und experimentellen Daten ist aus zweierlei Gründen essentiell, einerseits dienen experimentelle Werte der Validierung von Simulationen, andererseits können Simulationen dazu beitragen, Experimente korrekt zu interpretieren, oder sogar weitere Experimente anleiten. Insbesondere NMR Spektroskopie ist traditionell eng mit MD Simulationen verknüpft. Kapitel 3 beschreibt eine Methode, NMR Relaxationsparameter, speziell für Nuclear Overhauser (NOESY und ROESY) Spektren, basierend auf MD Simulationen zu berechnen. Dies ermöglicht eine Analyse des Einflusses interner Dynamik auf diese Spektren, was speziell für kleine, extrem flexible Moleküle wie Peptide von grossem Interesse ist. Eine solche Untersuchung wird in den Kapiteln 3 und 4 für zwei verschiedene β-Peptide durchgeführt.

Langreichweitige, elektrostatische Wechselwirkungen sind eines der Hauptprobleme und eine der Hauptlimitationen für MD Simulationen. Egal welche Methode zu ihrer (näherungsweisen) Behandlung man wählt, jede kann im Prinzip Artefakte hervorrufen. Zur Untersuchung solcher Artefakte in MD Simulationen mit explizitem Lösungsmittel kann man Methoden der Kontinuumselektrostatik heranziehen. Kapitel 5 beschreibt die Entwicklung eines Algorithmus zur Lösung der Gleichungen der Kontinuumselektrostatik für periodische Systeme, der auf schnellen Fourier Transformationen (FFTs) basiert. In Kapitel 6 werden verschiedene Methoden, elektrostatische Wechselwirkungen in MD

Simulationen zu berechnen, mit Hilfe dieses Algorithmus verglichen.

Bestimmung von Freien Energien und Entropien ist eines der Hauptziele von MD Simulationen. Kapitel 7 befasst sich mit verschiedenen Methoden, Entropien zu berechnen, und vergleicht ihre Anwendbarkeit mit Hilfe einfacher Testsysteme.

Kapitel 8 gibt einen kurzen Ausblick in die Zukunft.

Summary

Molecular dynamics (MD) simulations provide an atomic-resolution picture of molecular systems, which helps to understand structure and function of molecules of interest.

Chapter 1 gives a short overview of simulation techniques, particularly with respect to the approximations made to enable simulations of biomolecular systems. Additionally, several aspects of simulations are discussed: (*i*) application to biologically relevant processes, (*ii*) verification by comparison with experimental data, (*iii*) validation of the applied model and its approximations, and (*iv*) development of new techniques.

MD simulations contribute significantly to our understanding of the folding process of biomolecules, particularly proteins. Here, peptides serve as model systems, which are small enough so that reversible folding and unfolding can be observed in the simulations. With these studies one obtains information about the process of folding, the extent and composition of the unfolded state and the preferences of some sequences for particular secondary structure elements. In chapter 2, the dependence of the folding of a small, non-natural peptide formed by aminoxy acids on simulation conditions such as temperature and solvent is investigated.

Comparing simulation results with experimental data is essential for two reasons. First, experimental data are used to validate the simulations, on the other hand, simulations may help to interpret the experiments correctly, or may even guide further experiments. Especially NMR spectroscopy is very closely linked to MD simulations. Chapter 3 describes a method to compute NMR relaxation parameters, particularly for nuclear Overhauser (NOESY and ROESY) spectra, based on MD simulations. This back-calculation procedure makes an analysis of the influence of internal dynamics on NMR spectra possible, which is particularly interesting for small and highly flexible molecules such as peptides. Chapters 3 and 4 describe this type of analysis for two different β-peptides.

The treatment of long-range electrostatic interactions is one of the major problems and one of the main limitations for MD simulations. Any method can only be approximate and may in principle cause artifacts. One way to investigate such electrostatics artifacts in explicit solvent MD simulations makes use of the equations of continuum electrostatics. In chapter 5, an algorithm to solve the Poisson equation for periodic systems is developed and tested. In chapter 6, this algorithm is extended to various methods to compute electrostatic interactions in MD simulations and is used to compare these.

Calculating free energies and entropies is one of the major goals of MD simulations. Chapter 7 summarizes different methods to compute entropies and investigates their applicability for simple testsystems.

Publications

This thesis has led to the following publications:

Chapter 2:

Christine Peter, Xavier Daura, and Wilfred F. van Gunsteren,
"Peptides of aminoxy acids: a molecular dynamics simulation study of conformational equilibria under various conditions"
J. Am. Chem. Soc, **122**, (2000) 7461-7466

Chapter 3:

Christine Peter, Xavier Daura, and Wilfred F. van Gunsteren,
"Calculation of NMR-relaxation parameters for flexible molecules from molecular dynamics simulations"
J. Biomol. NMR, **20**, (2001) 297-310

Chapter 4:

Christine Peter, Magnus Rueping, Hans Jakob Woerner, Bernhard Jaun, Dieter Seebach, and Wilfred F. van Gunsteren,
"Molecular dynamics simulations of small peptides: can one derive conformational preferences from ROESY spectra?"
(2003) *submitted to Chem. – Eur. J.*

Chapter 5:

Christine Peter, Wilfred F. van Gunsteren, and Philippe H. Hünenberger,
"Solving the Poisson equation for solute-solvent systems using fast Fourier transforms"
J. Chem. Phys., **116**, (2002) 7434-7451

Chapter 6:

Christine Peter, Wilfred F. van Gunsteren, and Philippe H. Hünenberger,
"A fast-Fourier-transform method to solve continuum-electrostatics problems with truncated electrostatic interactions: algorithm and application to ionic solvation and ion-ion interaction"
(2003) *submitted to J. Chem Phys.*

Chapter 7:

Christine Peter, Chris Oostenbrink, Arthur van Dorp, and Wilfred F. van Gunsteren,
"Estimating entropies from molecular dynamics simulations"
(2003) *for submission to J. Chem. Phys.*

Related publications:

Wilfred F. van Gunsteren, Roland Bürgi, Christine Peter, and Xavier Daura,
"The key to solving the protein-folding problem lies in an accurate description of the denatured state"
Angew. Chem. Int. Ed., **40**, (2001), 351-355

Wilfred F. van Gunsteren, Roland Bürgi, Christine Peter, and Xavier Daura,
"Reply to the comment on the communication by van Gunsteren et al., Angew. Chem. Int. Ed. 40 (2001) 351-355"
Angew. Chem. Int. Ed., **40**, (2001), 4616-4618

Fred A. Hamprecht, Christine Peter, Xavier Daura, and Wilfred F. van Gunsteren,
"A strategy for analysis of (molecular) equilibrium simulations: configuration space density estimation, clustering and visualization"
J. Chem. Phys., **114**, (2001) 2079-2089

Wilfred F. van Gunsteren, Dirk Bakowies, Roland Bürgi, Indira Chandrasekhar, Markus Christen, Xavier Daura, Peter Gee, Alice Glättli, Tomas Hansson, Chris Oostenbrink, Christine Peter, Jed Pitera, Lukas Schuler, Thereza Soares, and Haibo Yu,
"Molecular dynamics simulation of biomolecular systems"
CHIMIA, **55**, (2001) 856-860

K. Anton Feenstra, Christine Peter, Ruud M. Scheek, Wilfred F. van Gunsteren, and Alan E. Mark,
"A comparison of methods for calculating NMR cross-relaxation rates (NOESY and ROESY intensities) in small peptides"
J. Biomol. NMR, **23**, (2002) 181-194

Xavier Daura, Alice Glättli, Peter Gee, Christine Peter, and Wilfred F. van Gunsteren,
"The unfolded state of peptides"
Adv. Prot. Chem., **62**, (2002) 341-360

Michael Bergdorf, Christine Peter, and Philippe H. Hünenberger,
"Influence of cutoff truncation and artificial periodicity of electrostatic interactions in molecular simulations of solvated ions: a continuum electrostatics study"
(2003) *submitted to J. Chem. Phys.*