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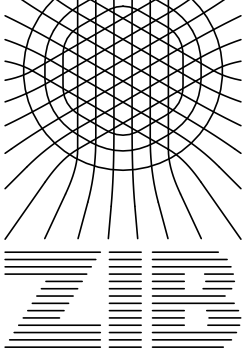

P. Deuflhard and S. Reich (eds.)

2nd International Symposium Algorithms for Macromolecular Modelling

May 21 – 24, 1997
Konrad-Zuse-Zentrum Berlin

Program and Collection of Abstracts

Preprint TR 97–03 (April 1997)

1 Themes and Goals

The symposium will bring together scientists from various branches of (applied), physics, chemistry, and biology who have been dealing with molecular dynamics and molecular modelling. The broad purposes of the symposium are (i) to provide an international forum for communicating state-of-the-art developments in molecular modelling algorithms, and (ii) to improve the prospects for future international collaborations by emphasizing the involvement of younger scientists from both sides of the Atlantic.

The main topics of the symposium are:

(i) Advanced timestepping in molecular dynamics

(ii) Quantum-classical dynamics

(iii) Free energy and ensemble calculations

(iv) Structure determination

(v) Electrostatics

2 Organization and Funding

The symposium is organized by B.R. Brooks, P. Deuflhard, W.F. van Gunsteren, J. Hermans, A. Mark, B. Leimkuhler, S. Reich, R.D. Skeel. The organizers gratefully acknowledge financial support from

- National Science Foundation (NSF)
- Deutsche Forschungsgemeinschaft (DFG)

3 Conference Program

Bracketed numbers following the title of the lecture/poster are corresponding section numbers where the abstract can be found. A list of all registered participants (as of April 24th) is given in Section 6.

3.1 General Schedule

Wednesday, May 21st

Time	Speaker	Title
9:00-10:00	Registration	
10:00-10:10	**P. Deuflhard**	Opening of the Symposium
10:10-11:10	**H.J.C. Berendsen**	Molecular Simulation of Biopolymers: Limits and Beyond (4.3)
11:10-11:30	Coffee Break	
11:30-12:15	**J. Hermans**	Protein-Small Molecule Interactions: From Energies to Free Energies (4.13)
12:15-2:00	Lunch	
2:00-2:45	**H. Scheraga**	Global Optimization and Protein Folding (4.29)
2:45-3:30	**Z. Wu**	Parallel and Global Molecular Distance Geometry (4.41)
3:30-4:30	Coffee Break	Poster Presentations
4:30-5:15	**J. Straub**	Algorithms for Global Energy Optimization of Complex Molecular Systems (4.38)
5:15-6:00	**D. Shalloway**	Hierarchical Mapping of Macromolecular Conformational Landscapes Using Macrostate Trajectory Diagrams (4.34)

Thursday, May 22nd

Time	Speaker	Title
9:00-9:45	**T. Schlick**	Recent Approaches to the Timestep Problem (4.30)
9:45-10:30	**R. Elber**	Computer Simulations of Long Time Dynamics of Biomolecules: A Path Integral Approach (4.9)
10:30-11:00	Coffee Break	
11:00-11:45	**B.J. Berne**	MD in Systems with Multiple Time Scales and with Long Range Interactions (4.4)
11:45:12:30	**B.R. Brooks**	Techniques for Macromolecular Simulation of Complex Systems (4.7)
12:30-2:00	Lunch	
2:00-2:45	**R.D. Skeel**	The Five Femtosecond Time Step Barrier (4.35)
2:45-3:30	**B. Leimkuhler**	Fast Symplectic–Reversible Integrators for Rigid Body Simulations (4.19)
3:30-4:30	Coffee Break	Poster Presentations
4:30-6:00	**Parallel Sessions**	
7:00-...	**Conference Dinner**	

Friday, May 23rd

Time	Speaker	Title
9:00-9:45	**K. Schulten**	Modelling Very Large Molecular Aggregates (4.32)
9:45-10:30	**K. Kuczera**	Exploring Multidimensional Free Energy Surfaces of Peptides and Proteins (4.18)
10:30-11:00	Coffee Break	
11:00-11:45	**H. Grubmüller**	Conformational Dynamics Simulations of Proteins (4.11)
11:45:12:30	**A. Mark**	Free Energy Differences From a Single Simulation of the Initial State (4.22)
12:30-2:00	Lunch	
2:00-2:45	**W.F. van Gunsteren**	Treatment of Periodic and Non-Periodic Long-Range Interactions in Molecular Dynamics Simulation (4.40)
2:45-3:30	**J. Board**	Multipole and Ewald Methods for Long Range Force Calculations in MD (4.5)
3:30-4:30	Coffee Break	Poster Presentations
4:30-6:00	**Parallel Sessions**	

Saturday, May 24th

Time	Speaker	Title
9:00-9:45	**M. Parrinello**	Ab-Initio Molecular Dynamics Calculation for Systems of Biological Interest (4.27)
9:45-10:30	**B. Lesyng**	Simulations of Complex Biomolecular Systems: Coupling of Microscopic and Mezoscopic Models and Theories (4.20)
10:30-11:00	Coffee Break	
11:00-11:45	**R.B. Gerber**	Quantum Molecular Dynamics Simulations of Large Polyatomic Systems (4.10)
11:45:12:30	**Ch. Schütte**	Quantum-Classical Molecular Dynamics: Theory and Numerics Including Nonadiabatic Effects (4.33)
12:30-2:00	Lunch	
2:00-2:45	**W. Yang**	Linear Scaling Quantum Mechanical Methods and Applications to Macromolecules (4.42)
2:45-3:30	**P. Jungwirth**	New Methods in Quantum Dynamics of Large Polyatomic Systems (4.16)
2:30-4:30	Coffee Break	Poster Presentations
4:30-6:00	**Parallel Sessions**	

3.2 Parallel Sessions

Thursday, May 22nd

Session A:

Time	Speaker	Title
4:30-5:00	**U. Ascher**	The Midpoint Scheme and Variants for Hamiltonian Systems: Advantages and Pitfalls (4.2)
5:00-5:30	**Ch. Lubich**	Exponential Integrators and Applications to Quantum/Classical Molecular Dynamics (4.21)
5:30-6:00	**D. Janezic**	An Efficient Split Integration Symplectic Method for MD Simulations of Complex Systems (4.15)

Session B:

Time	Speaker	Title
4:30-5:00	**J. Bohr**	Structure Transformations in Biomolecules Driven by Intrinsic Dynamics (4.6)
5:00-5:30	**J. Antosiewicz**	Molecular Electrostatic Properties of Protein Kinases and Phospatases at a Mezoscopic Level (4.1)
5:30-6:00	**V. Helms**	Conformational Energetics and Dynamics of Protein Kinases (4.12)

Friday, May 23rd

Session A:

Time	Speaker	Title
4:30-5:00	**H. Sklenar**	A New Approach to Macromolecular Electrostatics in Solution (4.36)
5:00-5:30	**O. Steinhauser**	Dielectric Component Analysis of Biopolymers (4.37)
5:30-6:00	**E.-W. Knapp**	A Monte-Carlo Method to Simulate the Protein Folding Process (4.17)

Session B:

Time	Speaker	Title
4:30-5:00	**A. Neumaier**	On the Construction of Residue Potentials for Protein Folding (4.25)
5:00-5:30	**M.Y. Tolstorukov**	Mathematical Model of the Conformational Transitions and Nonlinear Dynamics of the Nucleic Acid-Water System (4.39)
5:30-6:00	**S.V. Izvekov**	Polarons in Organic Crystals by Nonlocal Dynamical Coherent Potential Method (4.14)

Saturday, May 24th

Session A:

Time	Speaker	Title
4:30-5:00	**P. Nettesheim**	Quantum Classical Molecular Dynamics: Symplectic Integrators and Alternatives (4.24)
5:00-5:30	**R. Meier**	Applications of Ab-Initio MD Simulations in Chemistry and Polymer Science (4.23)
5:30-6:00	**B. Schmidt**	A Quantum/Classical Molecular Dynamics (QCMD) Approach to the Photodissociation Dynamics of Small Molecules in Rare Gas Clusters (4.31)

Session B:

Time	Speaker	Title
4:30-5:00	**D. Okunbor**	Efficient Parallel Methods for MD Simulations (4.26)
5:00-5:30	**D. Brown**	A Domain Decomposition Approach for General Purpose MD (4.8)
5:30-6:00	**J. Phillips**	Implementing Algorithms Transparently in a Message-Driven Parallel MD Code (4.28)

3.3 Poster Sessions

Participants of the meeting, who appear on a contributed poster, are printed in bold face.

Wednesday, May 21st

1. **P. Ahlström**, G. Wahnström, L. Torell: Low Frequency Vibrations in Monomere, Dimers and Polymers of Propylene Glycol (5.1)
2. **P. Bala, P. Grochowski, K. Nowinski, B. Lesyng**: New Developments in Quantum-Classical Molecular Dynamics. Applications to Enzymatic Reactions (5.3)
3. **N.K. Balabaev**, O.V. Gendelman, L.I. Manevitch: Numerical Simulation of Structural Defects in a Polyethylene Crystal (5.4)
4. **W. Bollweg**: Numerical Simulation of Crystal Structures by Simulated Annealing (5.5)
5. **P. Ding**, A. Shi, **Z. Zhou**: Computing Classical Trajectories of Diatomic Molecular Systems by Symplectic Algorithm (5.8)
6. **A. Lyubartsev**, A. Laaksonen: Calculation of Effective Interaction Potentials from Radial Distribution Functions. Applications to Macromolecular Systems (5.21)
7. **S.I. O'Donoghue**, M. Nilges: Use of Mean-Force Potentials for Protein Structure Prediction (5.28)
8. **M.Z. Qin**: Structure-Preserving Algorithms for Dynamical Systems (5.29)
9. **Z. Zhou, P. Ding**, S. Pan: Study of Classical Trajectories of H_2O in Chemical Reaction Dynamics (5.40)
10. **V.V. Andrushchenko**: Experimental Study and Theoretical Calculations of DNA-Me2+ Complexes Structure (5.2)

Thursday, May 22nd

1. **H. Böttcher**: MD Simulations Using Internal Coordinates (5.6)
2. **W. Carl**, G. Damaschun: Structure-Mobility Relation of Ribonuclease T1 (5.7)
3. **M. Eichinger**: FAMUSAMM: A new Algorithm for Rapid Evaluation of Electrostatic Interactions in MD Simulations (5.9)
4. **J. Gibson**: Simulation of Polymer Brushes using Dissipative Particle Dynamics (5.11)
5. **E.V. Hackl**, S. Kornilova, E. Kapinos, **V. Andrushchenko**, Yu. Blagoi: Interaction of DNA and its Components with Divalent Metal Ions in Solution with Different Water Activities – Model and Binding Constant Calculations (5.12)
6. **D. Hoffmann**: Monte Carlo Move Sets for Efficient Sampling of the Conformational Space of Biomolecules (5.14)
7. **S. Huo**: The MaxFlux Algorithm for Calculating Variationally Optimized Reaction Paths for Conformational Transitions in Many Body Systems (5.15)

8. **G.S. Jas**: Free Energy Simulations of Oxidative Damage to Calmodulin (5.16)

9. A. Kol, **B. Laird, B. Leimkuhler**: A Symplectic Method for Rigid-Body Molecular Simulation (5.18)

10. **A.S. Lemak**: The Collisional Dynamics Method for Molecular Dynamics Simulations (5.20)

Friday, May 23rd

1. **K. Kantiem, K. Nowinski**: Electrostatics of Biopolymers. A Finite Element Approach to a Poisson-Boltzmann Model (5.17)

2. **M.A. Mazo**, S.S. Sheiko, **N.K. Balabaev**: MD Simulations of Carbosilane Dendrimers (5.22)

3. **M. Meyer**, D. Schomburg: Protein Docking with Correlation Methods (5.23)

4. **K. Möhle, H.-J. Hofmann**: Perturbation of Second Structure of Small Peptides by N-Alkylated Amino Acids: A Theoretical Study (5.24)

5. **F. Nardi**: Local Interactions of Proline and Aromatic Residues in Short Peptides in Aqueous Solution: Database and Energetic Analysis Combine with Experimental Measurements (5.25)

6. **I. Neelov**, A. Darinskii, **N. Balabaev**, F. Sundholm: MD Simulation of Regular Polymer Networks (5.26)

7. **H.A. Ninaber**: Essential Dynamics on Mutated DNA (5.27)

8. T.M. Frimurer, G.H. Peters, J.J. Led, M.D. Sørensen, **O.H. Olsen**: Prediction of Side Chain Conformation in the Human a3-Chain Type VI Collagen C-Terminal Kunitz Domain: The Reorientation of the Trp21 Ring (5.10)

9. **A.L. Rabinovich**: Monte Carlo Simulations of Chain Molecules: Application of the Continuum Model to Intramolecular Bond Ordering (5.30)

10. A. Kolinski, **P. Romiszowski, A. Sikorski**: New Fast Algorithm for Lattice Simulations of Polymer Systems (5.19)

Saturday, May 24th

1. **H. Schäfer**: Extrapolation of Hydration Free Energies (5.31)

2. **D. Hilmer, Ch. Schmidt, E. Schmitt**: Hierarchical Methods in Structure Calculations of Large Biomolecules (5.13)

3. N. Severin, **B. Schürmann**: MD-Simulation of Polyethylene/Polypropylene Interfaces (5.32)

4. **J. Shelley**, M. Sprik, M.L. Klein: Simulations of a Surfactant Micelle Using a Polarizable Model (.33)

5. **V. Termath**: Ab-initio Molecular Dynamics Simulations of Chemical Processes in Macromolecular Environments (5.34)

6. **M. Thormann, K. Möhle, H.-J. Hofmann**: Conformational Properties of Peptides with Dehydroamino Acids (5.35)

7. **G.M. Ullmann, E.-W. Knapp**, N.M. Kostic: Modeling of the Plastocyanin-Cytochrome f-Complex. Simulations and Calculations of Electron-Transfer Pathways (5.36)

8. **M. Zacharias, H. Sklenar**: A Molecular Dynamics/Potential Annealing Approach to Build Amino Acid Side Chain Coordinates on a Semi-Flexible Protein Main Chain (5.37)

9. **P. Zdanska**: Quantum Dynamics of HCl Photodissociation in Ar12 Cluster (5.38)

10. **R. Zhou, B.J. Berne**, F.Figueirido, R.M. Levy: Large Scale Simulations of Solvated Proteins: Combining a Multiple Time Step Integrator with a Periodic Fast Multipole Method (5.39)

4 Abstracts for Talks

4.1 Molecular Electrostatic Properties of Protein Kinases and Phosphatases at a Mesoscopic Level

J. Antosiewicz(a), **E.Blachut-Okrasinska**(a), **B.Lesyng**(a), **J.M.Briggs**(b), and **J.A.McCammon**(b)
(a)ICM, Warsaw University, Pawinskiego 5A, 02-106 Warsaw, and Department of Biophysics, Warsaw University, 02-089 Warsaw, Poland
(b)Department of Chemistry and Biochemistry, University of California at San Diego, La Jolla, CA 92093-0365, USA

Protein kinases and phosphatases are signalling proteins which act in concert to control a variety of fundamental cellular processes. They phosphorylate or dephosphorylate other proteins. These processes are governed by electrostatic interactions, and are studied by us using a mezoscopic Poisson-Boltzmann model. The model, amongst others, allows to determine the most optimal ionization states of titratable residues and to correlate changes of the atomic charges with conformational transitions in the proteins. The macromolecular modelling methods allowed us to better understand the molecular features of these enzyme families.

4.2 The Midpoint Scheme and Variants for Hamiltonian Systems: Advantages and Pitfalls

U. Ascher
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The midpoint scheme, like higher order Gauss-collocation schemes, is algebraically stable and symplectic, and it preserves quadratic integral invariants. It appears particularly suitable for the numerical solution of highly oscillatory Hamiltonian systems, such as those arising in molecular dynamics, because there is no stability restriction when it is applied to a simple harmonic oscillator. Although it is well-known that the midpoint scheme may also exhibit instabilities in various stiff situations, one may still hope for good results when resonance-type instabilities are avoided.
In this paper we investigate the suitability of the midpoint scheme for highly oscillatory, frictionless mechanical systems, where the step-size k is much larger than the system's small parameter ε, in case that the solution remains bounded as $\varepsilon \to 0$. We show that in general one must require that k^2/ε be small enough, or else, even the errors in slowly varying quantities like the energy grow undesirably. The same holds for higher order collocation at Gaussian points. This restriction on k is still better than the best known for explicit schemes, where one must require $k = O(\varepsilon)$.
We also propose a new method for preserving the energy, as well as time-reversibility, for the long-time integration of non-stiff Hamiltonian systems.
This work was carried out in collaboration with S. Reich.

4.3 Molecular Simulation of Polymers: The Limits and Beyond

H.J.C. Berendsen
BIOSON Research Institute and Dept. of Biophysical Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

Molecular dynamics simulations of biopolymers as proteins and nucleic acids and of membranes and proteins in membranes can be realized for systems of several tens of thousands of atoms over

times of several nanoseconds. Future computers may extend the 'brute force' simulation times to hundreds of nanoseconds in the next decade. Present and future simulations will in first instance show the inadequacies of the force fields, but it is expected that these will be repaired when needed. Before long proper long-range treatments of electrostatics will be common practice, and atomic polarizability will be incorporated. Quantum treatment of reactive centers will become standard as well. But there is no hope that long time-scale events as slow phase changes, conformational transitions, protein folding, formation of large aggregates, and rheology on the second time scale, can be treated by straightforward dynamic simulation methods.
In this lecture first a video film will be shown of a large simulation: a porin trimer embedded in a lipid bilayer membrane in aqueous environment (70,000 atoms). Then the possibilities to reduce the dynamic complexity of a protein are discussed: these make use of a reduction of the number of degrees of freedom to a few essential cooperative ones (A. Amadei), or alternatively of the analysis of protein structure and dynamics in terms of a limited number of rigid bodies (S. Hayward). Finally a new approach called "dynamic density functional theory", developed by J. Fraaije and collaborators in Groningen, will be considerd. This theory considers the dynamic evolution of densities of particle species on the basis of spatial distribution of the chemical potential and is able to treat polymer dynamics on mesoscopic length scales and on time scales of seconds.

4.4 MD in Systems with Multiple Time Scales and with Long Range Interactions

B.J. Berne
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4.5 Multipole and Ewald Methods for Long Range Force Calculation in MD

J.A. Board
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We have implemented a number of variants of multipole- and Ewald-based methods for evaluating the long-ranged electrostatic forces in MD simulations. No one algorithm proves to be best in all cases; the most efficient choice depends on the uniformity of the system, the boundary conditions (periodic or not), and the degree of parallelism desired. We will show results from simulations of biomolecular systems where the strengths and weaknesses of each class of methods are evident. In general terms, Ewald-derived methods work well for periodic systems and a modest degree of parallelism; multipole methods perform well for free boundary conditions and when a high degree of parallelism is desired.

4.6 Structure Transformation in Biomolecules Driven by Intrinsic Dynamics

J. Bohr
Building 307, Depart. of Physics, DTU, Lyngby, DK–2800, Denmark

A model where structure transformations in biomolecules are driven by intrinsic dynamics is presented and it is explained how intrinsic dynamics also can be responsible for certain steps involved in the folding of proteins. The phenomenon is demonstrated by a very simple computer algorithm.

4.7 Techniques for Macromolecular Simulation of Complex Systems

B.R. Brooks
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4.8 A Domain Decomposition Approach for a General Purpose Molecular Dynamics Program

D. Brown
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To date the domain decomposition approach to parallelizing classical molecular dynamics (MD) simulations has largely been restricted to atomic systems. The complexity introduced by the connectivity in molecular systems has resulted in simpler to implement atom and force decomposition methods being used in preference. These techniques work well for a few processors but ultimately become communication bound as the number of processors increases. In this work we focus on the alternative domain decomposition approach in which particles are assigned to processors according to their positions in physical space. This allows the normal interaction potential truncations used in MD simulations to reduce the number of particles a processor needs to know about and thus restrict inter-processor communications to near-neighbour exchanges. Such a strategy naturally falls into a distributed-memory/message-passing model. Techniques will be discussed for identifying uniquely not only all possible pair interactions but all higher n-plets, e.g. triplets for bending potentials, quadruplets for torsions etc., and examples will be given for a program implemented on the Charles Hermite Centre Power Challenge Array in Nancy using the MPI protocol.

4.9 Computer Simulations of Long Time Dynamics of Biomolecules: A Path Integral Approach

R. Elber, **R. Olender**
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A new algorithm to compute long time molecular dynamics trajectories is presented (R. Olender and R. Elber, J. Chem. Phys.105, 9299 (1996)). The new algorithm profoundly extends the current (nanosecond) time scale accessible to atomically detailed computations to the much broader range of time-scales relevant to biophysics.
The new formalism is based on the stochastic path integral of Onsager and Machlup (L. Onsager and S.Machlup, Phys. Rev. 91,1505 (1953); S. Machlup and L. Onsager, 91,1512 (1953). Trajectories of fixed length of time are computed by path optimization between two end points. The formalism allows the calculation of approximate trajectories that are stable for an almost arbitrary time step, while keeping the full atomic description of the system.
The new formalism and the numerical algorithm for the trajectory optimization will be described. Several simple examples will be discussed first which include harmonic oscillator, double well system, and the Mueller potential. More elaborate cases that will be described are the axial to equatorial transition in alanine-dipeptide, folding of C-peptide and the R to T transition in hemoglobin.
We shall further discuss formalism (and perhaps examples) for calculations of time scales and rates using the above mentioned formalism.

4.10 Quantum Molecular Dynamics Simulations of Large Polyatomic Systems

R.B. Gerber(a),(b), **P. Jungwirth**(c), **E. Fredj**(a), **S. Gregurick**(a), **A.Y. Rom**(b)
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(c) J. Heyrovsky Institute of Physical Chemistry, Academy of Sciences of the Czech Republic, Dolejskova 3, 18223 Prague 8, Czech Republic

A recent method is presented for time-dependent quan- tum-mechanical simulations of the dynamics of many-atom systems. The method is applied to several systems and processes, including: (1) Photochemistry and spectroscopy of molecules solvated in large rare-gas clusters. (2) Energy transfer in collisions of large water clusters, (H2O)n, with atoms. (3) Spectroscopy and vibrational dynamics of peptides and of peptide-water complexes.
The algorithm begins with an approximation where classical Molecular Dynamics simulations are used to construct an effective, mean potential for each degree of freedom, and then quantum wavepackets for each mode are computed using these potentials. In an improved level of treatment, the above separable approximation (Classical Separable Potential method) is corrected for correlations between the modes. The full wavefunction is computed as a linear combination of terms, each of which is separable in the different modes (Configuration Interaction CSP). Classical MD simulations can be used in determining the terms that should be included, and which modes are strongly correlated, which drastically simplifies the calculations.
The applicability range of the Quantum MD simulation method, and possibilities of extensions and improvements are discussed.

4.11 Conformational Dynamics Simulations of Proteins

H. Grubmüller
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Computer simulations of the molecular dynamics (MD) of proteins provide fairly good descriptions of atomic motions in proteins, which allow to relate properties and function of proteins to microscopic processes (see, e.g., Ref. [1]).
However, such MD simulations require an enormous amount of computer time. Thus, even with a number of advanced techniques to speed up the simulations [2–4], only dynamical processes at time scales faster than a few nanoseconds can be described. In contrast, most biochemical processes like enzymatic catalysis, the gating of ion channels, or folding reactions occur at much slower time scales of microseconds to seconds and, therefore, are out of reach for conventional MD simulation techniques.
Viewed at slow time scales proteins are considerably more flexible than at the fast MD time scale, and a large variety of — typically collective — conformational transitions between distinct conformational substates is observed. Accordingly, the energy landscape of the conformational degrees of freedom exhibits a large number of iso-energetic local minima, which are separated by barriers [5]. In this scenario, only the lowest barriers are traversed in conventional MD simulations, whereas the larger transitions, which can be viewed as the 'elementary steps' of protein function, are, again, inaccessible.
We describe a technique, 'conformational flooding' [6], which enables the study of a large class of slow conformational transitions in atomic detail. The method destabilizes a given (initial) conformational substate during an MD-run in an unbiased manner, thereby accelerates slow transitions, and thus makes them observable even within relatively short simulations. The method is applied to relate the hierarchical structure of the conformational flexibility of a small

pancreatic protein to the underlying microscopic processes.

References

[1] Helmut Grubmüller, Berthold Heymann, and Paul Tavan. Ligand binding: Molecular mechanics calculation of the streptavidin-biotin rupture force. *Science*, 271(5251):997–999, 1996.
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[6] Helmut Grubmüller. Predicting slow structural transitions in macromolecular systems: conformational flooding. *Phys. Rev. E*, 52:2893, 1995.

4.12 Conformational Energetics and Dynamics of Protein Kinases

V. Helms, **J.A. McCammon**
Department of Chemistry and Biochemistry, University of California at San Diego, La Jolla, CA 92093-0365, U.S.A.

Protein function is often regulated by ligand induced conformational transitions. Although more and more three-dimensional structures are becoming available that show one protein in different conformations, not much is known about the underlying energetics and the time scales of these transitions. The catalytic subdomain of cAMP-dependent protein kinase is being considered a model system for the protein kinase family. Two peptide linkages connect its two domains and substrate binding is followed by a conformational transition from an 'open' protein conformation to a 'closed' conformation. We have calculated conformational free energies with the UHBD program [1] for a number of protein complexes in different conformations. Binding of ATP and a peptide inhibitor is shown to stabilize the closed state in a non-cooperative fashion. The dynamics of the system has been studied in atomic detail by stochastic dynamics simulations with a continuum treatment of the solvent [2].

[1] J.D. Madura et al. Comp.Phys.Comm. 91, 57 (1995).
[2] M.K. Gilson et al. J.Comp.Chem. 16, 1081 (1996).

4.13 Protein-Small Molecule Interactions: From Energies to Free Energies

J. Hermans, **Lu Wang**, **Li Zhang**
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We present a complete treatment for estimating free energies of formation of macromolecule-ligand complexes by transforming the ligand into a non-interacting state by gradually diminishing the forces between macromolecule (plus solvent) and ligand, in a molecular dynamics simulation. A specially designed potential ("molecular tweezers") is used to restrain the spatial position and orientation of the ligand molecule. Simulations with various rigid protein models allow estimates of components of the free energy of binding: the binding energy, the free energy for changing the shape of the protein to accommodate the ligand, and the free energy for loss of translational and rotational freedom of the ligand. Such simulations accurately reproduce the

free energy of binding of benzene, benzene derivatives, and Xe, Kr and Ar to a mutant of T4 lysozyme which contains a cavity of volume 160 $Å^3$.
Water molecules inside cavities in proteins constitute integral parts of the structure. We have sought a quantitative measure of the hydrophilicity of the cavities by calculating energies and free energies of introducing a water molecule into these cavities. A threshold value of the water-protein interaction energy at -12 kcal/mol was found to be able to distinguish hydrated from empty cavities. It follows that buried waters have entropy comparable to that of liquid water or ice. A simple consistent picture of the energetics of the buried waters provided by this study enabled us to address the reliability of buried waters assigned in experiments. We have developed the DOWSER program, which locates cavities inside a protein and assesses their hydrophilicity, given a set of coordinates.

4.14 Polarons in Organic Crystals by Nonlocal Dynamical Coherent Potential Method

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The nonlocal dynamical coherent potential approximation (NDCPA) is formulated to calculate a single-electron(exciton) Green's function of polaron due to the interaction of an electron(exciton) with (lattice or molecular) phonons in organic crystals. This approximation is an improvement of the dynamical CPA [1]. The NDCPA provides an efficient means of calculating of an approximate single-electron(exciton) Green's function in a case of a dynamical model of the Hamiltonian, in which an optical phonon spectrum and electron(exciton)-phonon coupling involving linear, quadratic or higher order with respect to the phonon operators terms are assumed. A set of recurrent equations is derived in the case of a system at zero temperature, from which the coherent potential as a function of energy E and wave vector k can be obtained. The simple algorithm for the polaron spectra calculations is obtained in the case of a linear electron(exciton)-phonon coupling, small electron(exciton) transfer, and with an assumption of only inelastic scatterings of electron(exciton) by phonons. If the energy of a vibrational relaxation is much larger of the electron(exciton) bandwidth the algorithm is allowed for the calculation of the lowest (localized) electron(exciton) state at the *arbitrary* electron(exciton) bandwidth. The algorithm is modified if the $n-$phonon short-range scatterings are relevant. For a more complex electron (exciton)-phonon coupling the recurrent equations which determine the coherent potential can be efficiently treated numerically.

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4.15 An Efficient Split Integration Symplectic Method for Molecular Dynamics Simulations of Complex Systems

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A new Split Integration Symplectic Method (SISM) for molecular dynamics (MD) simulations is described. The method involves splitting of the total Hamiltonian of the system into the harmonic part and the remaining part in such a way that both parts can be efficiently computed. The Hamilton equations of motion are then solved using the second order generalized leap-frog integration scheme in which the high-frequency motions are treated analytically by the normal mode analysis which is carried out only once, at the beginning of the calculation. The proposed method requires only one force evaluation per integration step, the computation cost per integration step is approximately the same as that of the standard leap-frog-Verlet method, and it allows an integration time step up to ten times larger than can be used by other methods

of the same order. The SISM was applied to MD simulations of the linear chain molecules as well to MD simulations of a box of water molecules, and was by an order of magnitude faster than the standard leap-frog-Verlet method. The approach for MD simulations described here is general and applicable to any complex system.

4.16 New Methods in Quantum Dynamics of Large Polyatomic Systems

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First quantum dynamical calculations going beyond separability approximation for a large polyatomic system are reported. The present method is a Configuration Interaction extension of the recently developed Classical Separable Potential approach (P. Jungwirth and R. B. Gerber, J. Chem. Phys. 102 (1995) 6046). The basic idea is to use first classical trajectories to guide the selection of important correlation terms and to simplify multidimensional integral evaluations for a subsequent fully quantum propagation. In this way, quantum dynamical simulations of good accuracy for systems of 100 and more modes, which is far beyond the current limit, become possible. Simulation of early dynamics following I2 photoexcitation in an Ar17 cluster reveal the collision induced breakdown of wavepacket separability and buildup of correlations, and the complex character of vibrational energy transfer from the I2 chromophore to the argon cage.

4.17 A Monte Carlo Method to Simulate the Protein Folding Process

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A new Monte Carlo (MC) method is presented which allows to simulate the folding process of small model peptides in a realistic manner. Key point of the method is the use of an all atom, off-lattice protein model with rigid bond lengths, bond angles and amide planes. Hence, the only degrees of freedom of the polypeptide backbone are the (phi,psi)-torsion angles. An elementary MC move is performed by co-operative rotations in a small window of consecutive amide planes, leaving the polypepetide conformation outside of the window invariant. These window MC moves generate local conformational changes only. Thus, large conformational changes of a polypeptide evolve gradually in time, if these MC moves are applied randomly many times.
To account for the lack of flexibility of the employed protein model a mean force is used for the (phi,psi)-torsion angles. It is derived from molecular dynamics (MD) simulations of a flexible dipeptide using conventional MD energy function. To avoid exaggeration of hydrogen bonding strengths for rigid polypeptide models, the electrostatic interactions involving hydrogen atoms are scaled down at short distances by 15% as compared to MD energy functions. With these adjustments of the energy function the rigid polypeptide model exhibits the same equilibrium distributions as does a fully flexible model with MD simulation.
The MC method is applied to a model peptide of 26 residues which represent the central part of the helix-turn-helix motive of ROP (Hoffmann & Knapp, 1996). Starting from a stretched beta-strand conformation pieces of alpha-helical structure form quickly. It follows a hydrophobic collapse in a compact conformation where the turn appears but is displaced. Then in a slow process of self-reptation the turn moves to its native-like position. The final conformation of the model polypeptide agrees with the ROP structure within the uncertainties of the energy function used.

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4.18 Exploring Multidimensional Free Energy Surfaces of Peptides and Proteins

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A new thermodynamic integration method is presented, enabling exploration of multidimensional conformational free energy surfaces of large flexible molecules. In this approach a single molecular dynamics simulation in which a set of coordinates has been constrained to fixed values yields the free energy gradient with respect to all coordinates in the set. set of coordinates has been constrained to fixed values yields the free energy gradient with respect to all coordinates in the set. The availability of the multidimensional gradient opens new possibilities for exploration of molecular conformational free energy surfaces, including free energy optimization to locate free energy minima, calculation of higher free energy derivatives, and finding optimal free energy paths between states. Additionally, choosing of all "soft" degrees of freedom as the constrained set leads to accelerated convergence of averages, effectively overcoming the sampling problem of free energy simulations. The method is applied to two systems:

Helical states of model peptides. For model peptides $(\mathrm{Ala})_n$ and $(\mathrm{Aib})_n$ where n=6,8,10 and Aib is α-methylalanine in vacuum, free energy maps and free energy optimization in $\phi - \psi$ space are used to locate free energy minima corresponding to α-, π- and 3_{10}-helical structures. The stability of the minima is characterized by calculating numerical second derivatives of the free energy. Free energy decomposition is employed to reveal the molecular mechanism for the numerical second derivatives of the free energy. Free energy decomposition is employed to reveal the molecular mechanism for the improved stability of the 310h relative to the ah in Aib-containing peptides.

DPDPE peptide pre-organization. For the linear form of the opioid peptide DPDPE in aqueous solution, the effective local sampling made possible by fixing all soft degrees of freedom is used to calculate the free energy difference between the open and cyclic-like structures, providing an estimate of the free energy of pre-organizing the peptide for disulfide bond formation. The open structure was found to be more stable by 4.0 ± 0.8 kcal/mol. The cyclic-like conformation was much better solvated than the open structure (by 39.2 kcal/mol); however, the open structure had more favorable intramolecular energy. The predicted low population of the biologically active cyclic-like structure is in qualitative agreement with the observed lower potency of the linear form of the peptide.

4.19 Fast Symplectic–Reversible Integrators for Rigid Body Simulation

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Recent research has demonstrated that symplectic and reversible integrators often have show exhibit much better long term stability than standard schemes. That the flow is symplectic means that the wedge product $dq \wedge dp$ of differentials is conserved; that the flow is time-reversible means that the Hamiltonian is invariant under the symmetry $p \to -p$.
The most obvious manifestation of nonsymplectic dynamics is drift in energy; when artificial measures such as velocity rescaling are used to conserve energy the destruction of phase-flow structure becomes apparent in other ways.
Constrained dynamics, such as occurs in molecular dynamics modelling when bond lengths are frozen, can be discretized using the SHAKE method [1], a generalization of the leapfrog method, a second order symplectic and reversible method [2]. The application of symplectic schemes to rigid body simulation requires the choice of an appropriate coordinate system. Quaternions

or Euler parameters prevent the use of efficient symplectic/ reversible discretizations. A better framework for rigid body simulation is a constrained particle model which is amenable to SHAKE discretization. A still better approach is based on integrating the dynamics of the rotation matrix, viewed as a dynamical object, subject to an orthogonality constraint. The latter formulation admits two symplectic-reversible discretization methods: (1) a SHAKE discretization enforcing the orthogonality constraint [3,5], and (2) a reduction-based explicit symplectic discretization [4,6]. Efficient implementation of these methods renders them competitive in terms of the step-step computational cost with standard schemes. Numerical experiments with rigid body water models show that both of these schemes easily outperform existing rigid body molecular dynamics methods in moderately long term simulations.
I will also describe an application to the simulation of the dynamics of an elastic rod, a simulation that incorporates a time-reversible variable stepsize strategy [7].

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4.20 Simulations of Complex Biomolecular Systems: Coupling of Microscopic and Mezoscopic Models and Theories

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Studies of structure and function of real biomolecular systems require harmonious applications of microscopic and mezoscopic theories and computational models. A brief overview of selected methods will be presented. For a more extensive review see [1,2] with references cited herein. Studies of large systems require a reduction of original many- dimensional models, which usually results in generation of effective interaction potentials. In quantum theories effective potentials for atomic motions appear when averaging over electronic degrees of freedom, see e.g. [3]. In turn, in classical theories a reaction field of solvent is generated when coming from a many-dimensional atomic description to a continuous field formalism. Models of complex enzymatic systems which make use of such potentials and introduce effective couplings between quantum and classical degrees of freedom will be discussed. In particular our Quantum-Classical Molecular Dynamics (QCMD) model [3-5] will be introduced. The model has been recently implemented on a massively parallel architecture and applied to an enzymatic reaction. Also, new extended versions of the QCMD model, namely Quantum-Gaussian Molecular Dynamics (QGMD) and Gaussian- Classical Molecular Dynamics (GCMD) will be briefly discussed. Regardless of the model which is applied to a time-dependent evolution of a biomolecular quantum-classical system, the system itself have to be well defined. In particular ionization states of all residues have to be properly assigned, which means that protons in the system should be placed in locations which minimize its total free energy. This can be done using a "titration procedure" based on a Poisson-Boltzmann equation. A case of a protein kinase [5] will be discussed as an example.
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4.21 Exponential Integrators and Applications to Quantum/Classical Molecular Dynamics

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The equations of motion in mixed quantum/classical molecular dynamics and the Car-Parrinello equations in ab initio molecular dynamics are both examples of oscillatory differential equations with dominating linear part, which one would like to integrate with long time steps that are not restricted, or only mildly restricted, by the highest frequencies in the system. We have developed *exponential integrators* for such problems. Their construction is based on the principle that they reduce to exact solvers for linear problems with constant coefficients. They invoke the action of the exponential or related functions of the Jacobian, which can be efficiently approximated using Krylov subspace techniques. A general-purpose exponential integrator has been made available in the code `exp4`. For the particular case of mixed quantum/molecular dynamics we have constructed a symmetric long-time-step scheme which can be rigorously shown to yield second order of accuracy independently of the highest frequencies. In the singular limit of the mass ratio tending to 0 the scheme tends to the Verlet discretization of the Born-Oppenheimer approximation. The talk is based on joint work with Marlis Hochbruck. The application to

quantum-classical MD is in cooperation with Christof Schütte and Peter Nettesheim.

4.22 Free Energy Differences From a Single Simulation of the Initial State

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In principle, the difference in free energy between a reference state and any other state of a system can be determined if the equilibrium fluctuations of the reference state are completely known. Essentially, the free energy of an alternative state can be extrapolated from the behavior of the system in the reference state. For many applications, most notably in structure based drug design, such an approach has many advantages. One is that a single simulation (ensemble) can be used to estimate free energy differences to multiple alternate states.
Methods to estimate the change in free energy associated with multiple perturbed states from a single, or a small number of simulations are based on either: (i) a series expansion of the free energy around a given reference state, (ii) an assumption with respect to the functional form of the free energy or, (iii) the application of the thermodynamic perturbation formula.
The implementation of the methodology in GROMOS96 and the application of extrapolation approaches to a series of problems ranging from a simple diatomic molecule to protein-ligand interactions will be discussed.

4.23 Applications of Ab-Initio Molecular Dynamics Simulations in Chemistry and Polymer Science

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Results from quantum MD simulations on various catalytic reactions will be presented, including olefin polymerisation using metallocene catalysts, and simulations aiming for the ultimate mechanical properties of polymers.

4.24 Quantum Classical Molecular Dynamics: Symplectic Integrators and Alternatives

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It was revealed that the QCMD model has a canonical Hamiltonian structure [3], which implies symplecticity and the conservation of energy. An efficient and reliable integrator, which passes these properties to the discrete solution is the symplectic and explicit PICKABACK algorithm [2].
The only drawback of this kind of integrator is the small stepsize in time induced by the splitting techniques used to discretize the quantum evolution operator. Recent investigations based on [1] result in alternative approaches which overcome this difficulty for a wide range of problems. By using iterative methods in the evaluation of the quantum time propagator, these techniques allow the stepsize to adapt to the coupling between the classical and the quantum mechanical subsystem. This yields a drastic reduction of the numerical effort.
The pros and cons of both approaches as well as the suitable applications will be distinguished in the last part of the talk.

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4.25 On the Construction of Residue Potentials for Protein Folding

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I shall discuss recent attempts of our research group to construct a smooth potential for use in off-lattice protein folding studies. Our potential is a function of the amino acid labels and of the distances between the C_α atoms of a protein, with a cutoff at 12 Angstrom.
To find appropriate empirical pair potentials from the known protein structures in the Brookhaven Protein Data Bank, it is necessary to calculate smooth densities for the distance distribution of C_α-atoms at given bond distance d and given residue assignments a_1, a_2. The potentials then emerge as the negative logarithm of the densities. Since a huge number of pair potentials are required, fully automatic and reliable density estimators are necessary.
The accuracy of the densities is low, theoretically at best $O(1/\sqrt{n})$ for a sample of size n, but in practice often much lower. For example, histogram estimates as used in the work on z-scores by Sippl's group have, for the optimal bin size, the extremely poor accuracy of $O(n^{1/10})$ only.

This requires the grouping together of data for 'similar' triples (d, a_1, a_2), a task we perform by means of a regression tree classifier.
Moreover, automatic estimation is difficult as the traditional statistical techniques for density estimation usually require the interactive selection of some smoothing parameter (such as the bin size). Finally, the smoothness requirement produces additional difficulties in the neighborhood of the cutoff threshold that need to be overcome. After many false starts, we now believe to have a reasonably reliable pair potential estimator.
We also discuss the construction of smooth and quickly computable surface terms modeling solvent interactions, and how to find appropriate weights with which the various terms enter the total potential.

4.26 Efficient Parallel Methods for Molecular Dynamics Simulations

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The study of many-particle systems has increased significantly over the past decade, because of the increasing number of useful applications it supports. Numerical experiences have shown that the force calculation contributes ninety percent of the total simulation time. This is an $O(N^2)$ algorithm, mainly due to pairwise interactions, where N is the number of particles in the system. The interaction decomposition technique proposed by Taylor *et al.* uses a special mapping scheme and optimal communication to reduce the overall computation time. In this paper, we propose two algorithms based on the force decomposition approach. The first technique which we call Force-Row Interleaving (FRI) method, treats rows once at a time and the other approach, called Force-Stripped Row (FSR), computes *a priori* the block of rows that balances workload to be sent to a processor. These two algorithms were tested on a system of 32000 atoms of liquid argon and implemented on a distributed memory, 16-processor iPSC/860. The FRI and FSR were both comparable to existing parallel techniques with efficiencies of 98.18% and 98.63%, respectively.

4.27 Ab-Initio Molecular Dynamics Calculation for Systems of Biological Interest

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Algorithmic developments, combined with the power of parallel computing, allow the ab-initio study of relatively large systems of relevance to biology. We describe here extensive studies on the properties of water and water solutions. We also assess the ability of the method to reproduce the structure of self assembled peptides and RNA. Finally results on the spin-structure relation in the heme prostetic group will be presented.

4.28 Implementing Algorithms Transparently in a Message-Driven Parallel MD Code

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Parallel molecular dynamics programs employing shared memory or replicated data architectures encounter problems scaling to large numbers of processors. Spatial decomposition schemes offer better performance in theory, but often suffer from complexity of implementation and difficulty in load balancing. In the program NAMD 2 we have addressed these issues with a hybrid decomposition scheme in which atoms are distributed among processors in regularly sized patches

while the work involved in computing interactions between patches is decomposed into independently assignable compute objects. When needed, patches are represented on remote processors by proxies. The execution of compute objects takes place in a prioritized message-driven manner, allowing maximum overlap of work and communication without significant programmer effort. In order to avoid obfuscation of the simulation algorithm by the parallel framework, the algorithm associated with a patch is encapsulated by a single function executing in a separate thread. Output and calculations involving reductions are similarly isolated in a single thread executing on the master node. This combination of features allows us to make efficient use of heterogeneous clusters of multiprocessor workstations while presenting minimal barriers to method development and implementation.

4.29 Global Optimization and Protein Folding

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The computational aspects of the protein folding problem involve the minimization of an empirical potential energy function. Such minimization, however, leads only to the local minimum closest to the starting point. The potential energy landscape is a very complicated one in a multi-dimensional space, and several algorithms have been developed to locate the global minimum in such a space. The progress of such global optimization techniques, applied to the protein folding problem, will be discussed. These global optimization methods are also applicable to other physical problems, e.g. some problems in X-ray crystallography, and these too will be discussed.

4.30 Recent Approaches to the Timestep Problem

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Innovative algorithms have been developed during the past decade for simulating Newtonian physics for macromolecules. A major goal is alleviation of the severe requirement that the integration timestep be small enough to resolve the fastest components of the motion and thus guarantee numerical stability. This timestep problem is challenging if strictly faster methods with the same all-atom resolution at small timesteps are sought. Mathematical techniques that have worked well in other multiple-timescale contexts — where the fast motions are rapidly decaying or largely decoupled from others — have not been as successful for biomolecules, where vibrational coupling is strong.
This talk will review general issues that limit the timestep and describe available methods (constrained, reduced-variable, implicit, symplectic,multiple-timestep, and normal-mode-based schemes). Our dual timestep method LN (for its origin in a Langevin/Normal Modes algorithm) will also be presented and recent results presented (joint work with E. Barth and M. Mandziuk). LN relies on an approximate linearization of the equations of motion every Δt interval (5 fs or less), the solution of which is obtained by explicit integration at the inner timestep $\Delta\tau$ (e.g., 0.5 fs). Since this subintegration process does not require new force evaluations, LN is computationally competitive, providing 4–5 speedup factors, and results in good agreement, in comparison to 0.5 fs trajectories. In combination with force splitting techniques, even further computational gains can be achieved for large systems.

4.31 A Quantum/Classical Molecular Dynamics (QCMD) Approach to the Photodissociation Dynamics of Small Molecules in Rare Gas Clusters

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The photodissociation dynamics of HX/ DX (X = F, Cl, ...) molecules in the environment of a rare gas (Rg) cluster is investigated. Model system are ranging from the "one atom solvent" case HXRg [1, 2] to one (or more) complete icosahedral solvation shells $HXRg_n, (n = 12, 54, \ldots)$ [3]. The principal motivation for this computational study is to model the process of cage exit versus recombination of the light photofragment (H) as well as the evaporation of solvent particles (Rg) from the cluster. Special emphasis will be on the dependence of the dissociation dynamics on the initial quantum state of the HX molecule ("vib–rotationally mediated chemistry"[4]).
The present study also serves the purpose of developing an efficient and quantitative theoretical tool for the description of fast quantum dynamical processes in condensed phases. For the model systems mentioned above, we solve the three–dimensional time-dependent Schrödinger equation for the quantum dynamics of the light photofragment (H-atom) while the coupling to the dynamics of the heavy atom is modelled by a quantum/classical molecular dynamics (QCMD) approach [5, 6, 7] using a new symplectic integration scheme [8]. The accuracy of the QCMD approximation is checked by comparison against a full quantum treatment.

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4.32 Modelling Very Large Molecular Aggregates

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Biomolecular aggregates are often the smallest functional units in biological cells and their disease states. Examples are membranes and their complexes with bioenergetic proteins, the nucleosome interaction with regulatory proteins, and capsids containing viral RNA. The mere size of most aggregates precludes their modelling for most biomedical researchers, but parallel computing can come to the rescue. We have explored the use of workstaion clusters computing, developed a unified software system MDScope to model as well a view large structures, and introduced new theoretical concepts and algorithms adequate for ultra large systems. Recently completed demanding and particularly relevant applications will be presented.

4.33 Quantum-Classical Molecular Dynamics: Theory and Numerics Including Nonadiabatic Effects

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In molecular dynamics applications there is a growing interest in *mixed quantum-classical* models. This talk is concerned with two of these models: the *adiabatic* or Born–Oppenheimer (BO) model and the so–called QCMD model. Both models describe most atoms of the molecular system by the means of classical mechanics but an important, small portion of the system by the means of a wavefunction. In the BO model this wavefunction is *adiabatically* coupled to the classical motion while the QCMD model consists of a *singularly perturbed* Schrödinger equation nonlinearly coupled to the Newtonian equations. Under certain conditions both models are known to approximate the full quantum dynamical evolution of the system [1,2,3]. These results will be summarized in the first part of the talk.
In contrast to the BO model, the QCMD model includes *nonadiabatic* processes, e.g., transitions between the energy levels of the quantum system or resonance effects near level crossings. It will be shown that and how, in mildly nonadiabatic scenarios, QCMD simulations yield good approximations of nonadiabaticity in full quantum dynamics.
The talk's last part will present some recently developed algorithms for QCMD simulations. These algorithms are based on direct computation of the quantum propagation via iterative techniques and include an adaptive control of the stepsize of each time step. In comparison to standard techniques these approaches lead to speed-up factors of up to 100 if the classical motion allows large stepsizes.

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4.34 Hierarchical Mapping of Macromolecular Conformational Landscapes Using Macrostate Trajectory Diagrams

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Macromolecular conformational transitions (e.g., folding) are phenomenologically described by master equations for metastable, macroscopic states (e.g., unfolded state, molten globule, folded state). The "macrostates" are temperature-dependent regions of conformation space that are effectively isolated by energy barriers that are high on a scale set by the temperature. However, the identification and description of macrostates is difficult because of the high dimensionality and jaggedness of the energy landscapes. Instead, conformational subspaces are often described using "order parameters" (e.g., number of native contacts). But these ad hoc measures usually do not resolve the intrinsic, though hidden, macrostates embedded in the conformation space. Thus, they are not adequate for determining experimental kinetic and thermodynamic relationships.
Starting from a simple stochastic model of macromolecular motion, we show how macrostates can be algorithmically identified by non-linear "characteristic packet equationsthat determine the centroids and fluctuation tensors of isolated concentrations of ensemble probability density. In practice, the packets, which provide zeroth-order approximations to the macrostates, are hierarchically identified by recursive subdivision of the conformation space during annealing from high to low temperature. The resultant "macrostate trajectory diagram" is a tree-like

description of the hierarchical relationships between the temperature-dependent macrostates. It permits thermodynamic (e.g., free-energies) and kinetic (e.g., transition activation energies) parameters to be computed by efficient coarse-grained sampling methods that are matched to the temperature-dependent spatial scales of the macrostates. The diagrams also provide coarse-grained "road-maps" for guiding and evaluating computational search algorithms. The approach is illustrated using small peptides.

4.35 The Five Femtosecond Time Step Barrier

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This talk describes joint work with T.C. Bishop and K. Schulten, joint work with B. Garcia-Archilla and J.M. Sanz-Serna, and new work. Numerical experiments are performed on a 36,000-atom protein–DNA–water simulation to ascertain the effectiveness of multiple time stepping (MTS) for reducing the time spent computing long-range electrostatics interactions. It is shown for the Verlet-I/r-RESPA MTS, which is based on approximating long-range forces as widely separated impulses, that a long time step of 5 fs results in a dramatic energy drift. Moreover, this is less pronounced if one uses a yet larger long time step! The cause of the problem can be explained by exact analysis of a simple two degree-of-freedom linear problem, which predicts numerical instability if the time step is just less than half the period of the fastest normal mode. To overcome this, we propose a modification of the impulsive Verlet-I/r-RESPA method, which we call the mollified impulse method. The idea is that for the slow part of the force one uses the gradient of the slow part of the potential energy modified so that it is evaluated at averaged values of the positions. We are currently implementing the algorithm for water and hope to have results by April 15. In particular, we wish to test a variant of the idea suggested by S. Reich.

4.36 A New Approach to Macromolecular Electrostatics in Solution

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The field integrated electrostatic approach (FIESTA) solves the boundary problem of the linear Poisson-Boltzmann equation in terms of analytically calculated virtual sources in the interior volume of the molecule. Reaction field energies and forces of comparable accuracy are obtained at least two orders of magnitude faster than with presently available programms. The source representation and the computational speed of the algorithm allow to include electrostatic solvent effects in molecular force fields of computer simulations. Analytic derivations and approximations as well as accuracy and timing of the new algorithm will be discussed in the context of applications of molecular systems of different size.

4.37 Dielectric Component Analysis of Biopolymers

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Research in this group has traditionally focused on the correct treatment of electrostatic interactions in computer simulations (molecular dynamics (MD) and Monte Carlo (MC) calculations), and, more recently, on a deeper understanding of the dielectric properties of solvated biopolymers. Recent methodological developments combined with new results warrant further research

in both areas. Consequently, the this contribution consists of two distinct, but interrelated parts: (i) A critical test of the role of dielectric boundary conditions in simulations using the Ewald summation method, and (ii) the experimental verification of a new approach to decompose the dielectric properties of biopolymers. The application of this decomposition to biopolymers is expected to lead to an enhanced understanding of the role of electrostatics in biological systems.
Computer simulations have become an indispensable tool in biophysics, structural molecular biology and rational drug design. Correct calculation of the interaction terms is a prerequisite for meaningful results, as well as for the critical evaluation and improvement of the force-fields, on which all such methods rely. The proposed critical investigation of the role of dielectric boundary conditions in connection with the Ewald summation technique represents a contribution to this area of research. The goal is to detect artifacts due to the current implementation of the Ewald summation method (or, more correctly, the dielectric boundary conditions which result from this implementation) and to provide an efficient, yet consistent computation of electrostatic interactions in computer simulations.
Simulation methods are used to predict quantities that either cannot be measured directly or when accurate experimental data are difficult to obtain. They are also helpful for the interpretation of experimental results since in a simulation the system of interest can be studied in detail on the molecular level. A new algorithm is presented and tested which makes possible the separate description of the dielectric properties of a system consisting of a biopolymer, water and counter-ions. Such a decomposition is an excellent example of the use of computer simulations for analysis that is difficult to achieve experimentally. Due to recent, improved experimental techniques, however, a semi-quantitative verification of the proposed method should be possible for selected model systems.

4.38 Algorithms for Global Energy Optimization of Complex Molecular Systems

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The potential energy surface of a molecular cluster or biomolecule is rugged with a large number of local minima. Finding the lowest energy conformation can be very challenging. A number of promising algorithms designed to solve this "multiple minima problem" will be described.
One class of algorithms is based on the paradigm of potential energy smoothing. The potential surface is transformed into a smoothed surface with few energy minima. These minima are isolated and then followed as the transformation is reversed and the original potential surface is recovered.
In another class of algorithms, the system configuration is represented by a continuous wave function. Planck's constant is set to a very large value such that the ground state of the system is delocalized. The system's ground state is then followed as Planck's constant is reduced to zero (or its physical value) where the system density is localized in the lowest energy minimum. This process is referred to as quantum mechanical annealing.
Finally, a Monte Carlo simulated annealing algorithm which employs an acceptance criterion based on non-Gibbs-Boltzmann (Tsallis) statistics is described.
Applications of the above methods to the energy optimization of model heteropolymers and all atom models of peptides are discussed.

4.39 Mathematical Model of the Conformational Transitions and Nonlinear Dynamics of the Nucleic Acid - Water System

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The mathematical model of the trigger type has been suggested to simulate the nucleic acid - water system. The analysis of the kinetic equations of the sorption and conformational transition processes and the analysis based on the nonlinear master equations show a non-trivial bifurcation behavior of the system which leads to the bistability, and this allows one to explain sorption and conformational hysteresis experimentally observed. Besides, autowave processes, such as traveling fronts of a new conformation (trigger waves), are possible in the corresponding spatially extended system, if diffusion of water molecules is taken into account.

4.40 Treatment of Periodic and Non-Periodic Long-Range Interactions in Molecular Dynamics Simulation

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In the past a variety of methods has been used in molecular simulation to approximate the long-range electrostatic interactions. The most efficient schemes are (i) plain cut-ff, (ii) cut-off with (Poisson-Boltzmann) reaction field and (iii) particle-particle particle-mesh (P3M). All suffer from drawbacks: neglect or use of a mean field approximation beyond an atom-atom or charge-group charge-group cut-off or the introduction of artificial periodicity. The effects of the application of the different techniques and a P3M method with non-periodic long-range interactions are considered.

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[3] B.A.Luty, I.G.Tironi and W.F. van Gunsteren Lattice-sum methods for calculating electrostatic interactions in molecular simulations J.Chem.Phys. 103 (1995) 3014-3021
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[5] P.H.Hunenberger and W.F. van Gunsteren Alternative schemes for the inclusion of a reaction=field correction into molecular dynamics simulations: influence on the simulated energetic, structural and dielectric properties of liquid water. submitted to J.Chem.Phys. (1997)

4.41 Parallel and Global Molecular Distance Geometry

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We present our work on developing global continuation algorithms and software for the solution of molecular distance geometry problems. We describe the algorithms and their implementation on massively parallel architectures and local networks of workstations. We show how the continuation algorithms, based on global smoothing, are used to obtain exact or approximate solutions to the distance geometry problems. The smoothing transform is computed with Gauss-Hermite approximation. Efficient optimization algorithms are used to trace the minimizers in continuation including trust region, variable-metric limited-memory, and truncated Newton. We present

the test results on problems for protein structure determination and discuss issues yet to be addressed for large and practical applications.

4.42 Linear Scaling Quantum Mechanical Methods and Applications: Macromolecules in Solutions

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This talk is devoted to the description of how the linear scaling methods can be achieved for some of the most popular electronic structure methods, ranging from semiempirical quantum chemical methods, to the first-principle Hartree-Fock method and density functional theory. Progress will be presented in the development of linear scaling approaches for the three major computational tasks: the solution of the eigenvalue equation, the construction of the Hamiltonian matrix and the description of solvent effects. Applications to the study of the solvent polarization and the electronic structure of biological macromolecules at the semiempirical level will be described.

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5 Abstracts for Posters

5.1 Low Frequency Vibrations in Monomere, Dimers and Polymers of Propylene Glycol

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We have studied the low-frequency dynamics of oligomers ($n = 1$ and $n = 2$) and polymers ($n = 45$) of propylene glycol using Molecular Dynamics (MD) simulations. A polymer structure was built from a Reverse Monte Carlo (RMC) simulation of the static structure factors for poly(propylene oxide) from neutron diffraction and used as a starting structure for molecular dynamics simulations of the polymer. The shorter-chain oligomers were simulated using random starting structures. The simulations were performed at temperatures both below and above the the glass transition temperature. The vibrational density of states (DoS) was calculated together with other structural and dynamic properties.

Our results indicate that the low-frequency peak below 100 cm^{-1}, generally referred to as the boson peak, is to a large extent due to *inter*molecular degrees of freedom, the peak position and shape being rather insensitive to changes of the intra-chain dynamics.

5.2 Experimental Study and Theoretical Calculations of DNA-Me2+ Complexes Structure

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The films of DNA complexes with Mn2+,Cu2+ and Ca2+ ions at relative humidities 5-98spectroscopy method. The theoretical calculations in the frame of the semiempirical model of intermolecular interactions were made. It were revealed the sites of preferential cation binding to nucleic bases. It was obtained that Mn2+ and Ca2+ ions form with DNA following complexes: N7-Mn2+(Ca2+)-O6, N7- Mn2+(Ca2+)-H2O-O6 of guanine and helates with phosphate groups and H2O molecules both directly and through water while Cu2+ ions form helates with nitrogen base groups: O6 and N7 of guanine and O2 and N3 of cytosine.

5.3 New Developments in Quantum-Classical Molecular Dynamics. Applications to Enzymatic Reactions

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We implemented an extended version of our Approximate Valence-Bond method into the Quantum-Classical Molecular Dynamics model. The QCMD/AVB formalism was used to simulate several steps of an enzymatic reaction. Visualization of the quantum-dynamical simulation results allowed to better understand a nucleophylic substitution reaction in the enzyme active site. In parallel, we have been developing modified versions of the QCMD model using Gaussian wave packets. This allows either to treat the classical degrees of freedom in a semiquantum way or to represent the time-dependent wave function as a linear combination of the Gaussian wave packets. Such combination can be easily propagated in a parameter space to satisfy variational, quantum-dynamical equations of motion. The extended versions of our present QCMD model

are called Quantum-Gaussian Molecular Dynamics (QGMD) or Gaussian-Classical Molecular Dynamics (GCMD), respectively.

5.4 Numerical Simulation of Structural Defects in Polyethylene Crystal

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Structural defects of different types are known from an analytical investigation of a polyethylene crystal, but a numerical simulation seems to be the only available way to study their stability, mobility and other properties. In the present paper such investigation was undertaken for a model of monoclinic polyethylene crystal with CH2-groups considered as united atoms.
The structural defects investigated were domain walls (cooperative twist of the polyethylene chains) and point defects-vacancies (elongation and twist of one chain in the field of neighbours). These defects were prescribed to the model system and then the static and dynamics of the crystal with defect were studied by molecular dynamics simulation.
It was established that the twist is localized at some space scale independent on the size of the system. The size of the defects corresponds to the theoretical predictions. The both types of defects are stable and movable without considerable discreteness barrier.
The new properties discovered by means of the numerical simulation are:

- the existence of domain walls with different angles to the chain axes;
- the unique velocity of motion of the vacancies.

5.5 Numerical Simulation of Crystal Structures by Simulated Annealing

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We apply Simulated Annealing techniques to search for the minimum energy structure of potential energy functions associated with crystal structure. Most approaches require detailed a priori knowledge of the structure. We propose suitable energy functions for determining correct structures in a variety of ionic crystals. These functions incorporate rules from electrostatics and crystal chemistry but do not assume knowledge of internal symmetries. We discuss an improved Simulated Annealing variant and present several examples of predicted crystals.

5.6 MD-Simulations Using Internal Coordinates

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The common programs for MD-simulations of proteins and other macromolecules (for instance the program CHARMm) use Newton's equations in Cartesian coordinates to simulate the dynamical behavior of the molecular system. The equations of motion from Abagyan [1] use internal coordinates (i.e. bond lengths, bond angles, and torsion angles) to describe conformational changes of macromolecules. The method allows it to freeze arbitrary internal degrees of freedom of the molecule. Thus the high-frequency vibrations of the bond lengths and bond angles can be neglected and consequently the size of the timestep for the integration of the equations of motion could be increased. The method was applied to a model system with two

torsion angles as internal degrees of freedom. The conservation of energy was tested. The uneven distribution of torsion angles which is due to the specific constraints from the eliminated degrees of freedom was examined. This problem relates to the so called metric tensor effects and the Fixman potential [2].

[1] R. Abagyan and V.E. Dorofeev, *J. Chem. Phys.*, **92**, 261–272, 1991.
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5.7 Structure-Mobility Relation of Ribonuclease T1

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We calculated the expectation value of the radius of gyration and the Stokes radius of Ribonuclease T1 with two disulfide bridges in the denatured state. The calculation of the denatured state yields a hydrodynamic interaction parameter (on the preaveraged Oseen level) of $h = 0.17$. This was used for the evaluation of the mobility of the bridged chain. The obtained results show good agreement with data obtained from dynamic light scattering. It could be shown that denatured Rnase T1 is a random coil.

5.8 Computing Classical Trajectories of Diatomic Molecular System by Symplectic Algorithm

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Classical trajectories of diatomic molecular systems have been computed by means of both symplectic and Runge-Kutta algorithms. It is shown that the energies of the systems computed by symplectic algorithm are kept unchanged till one million steps (about 10^{-10}s), and the trajectories are always identical with physical analysis. However, the energies computed by Runge-Kutta algorithm are irregular and unpredictable, and the trajectories are different from physical analysis. Therefore, symplectic algorithm is one of the reasonable methods for calculation of the classical trajectories of the micro chemical reaction dynamics.

5.9 FAMUSAMM: A new Algorithm for Rapid Evaluation of Electrostatic Interactions in Molecular Dynamics Simulations

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Within MD simulations the exact evaluation of long-range Coulomb interactions is computational demanding and becomes prohibitive for large systems. We have developed an efficient and yet sufficiently accurate approximative scheme which combines the structure-adapted multipole method (SAMM) with a multiple-time-step method. The computational effort for MD simulations required within our new method FAMUSAMM scales linearly with the number of particles.

5.10 Prediction of Side Chain Conformation in the Human a3-Chain Type VI Collagen C-Terminal Kunitz Domain: The Reorientation of the Trp21 Ring

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Structural information on the human a3-chain type VI collagen C-terminal Kunitz domain has been obtained by x-ray crystallography and nmr spectroscopy. In general the structures determined by the various methods are very similar and resemble the well known BPTI structure. However, the NMR spectroscopic data show that one particular side chain, Trp21, has two distinct conformations referred to as the major and the minor conformations, respectively. In the x-ray crystallographic structure the major conformation is observed exclusively. Based on the nmr intensities of the corresponding signals in the two conformations it is found that the population of the minor conformation is 6.4% of the major conformation. Due to lack of NOEs corresponding to the minor conformation detailed structural data are missing for this conformation.

Using an adiabatic map procedure, the minor conformation is predicted as well as a transition pathway indicated. Evidence of the predicted minor conformation is further substantiated by:

1. Estimation of the free energy difference between the major and minor conformation which matches the experimentally determined population densities.

2. Calculation of chemical shifts due to ring currents in the major and minor conformation. Good agreement is observed to experimental data.

Further, molecular dynamics (MD) simulations of the two structures have been undertaken. Analysis of the MD trajectories has been performed using the Essential Dynamics method.

5.11 Simulation of Polymer Brushes Using Dissipative Particle Dynamics

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Dissipative Particle Dynamics (DPD) introduces a lattice-gas automata time-stepping procedure into a molecular-dynamics scheme. This very young technique combines the modelling flexibility of molecular dynamics with the computational efficiency of lattice-gas automata schemes. Polymer brushes consist of long-chain polymer molecules attached at one end to a surface or interface at a density high enough such that the chains are forced to stretch away from the interface. This presentation shows how DPD may be used to model polymer brushes, using bead-and-spring type presentations of the chains.

5.12 Interaction of DNA and its Components with Divalent Metal Ions in Solution with Different Water Activity - Model and Binding Constant Calculations

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The interaction of Cu2+, Mn2+ and Ca2+ ions with DNA macromolecule was studied in the solutions with different water activity at different metal ion concentration by IR- spectroscopy. For all the DNA absorption bands the sharp increase of band intensity in the narrow range of metal ion concentration is observed. Such effect may be conditioned by high cooperativity of the process of the metal ions binding to the DNA. This is, probably, due to effects of aggregation or compactisation of the DNA macromolecule. This process has a cooperative character, similar for all investigated ions. The binding isotherms are of nonmomotonous character similar for the Van- der-Waalse isotherms for phase transitions liquid-vapour. Such DNA transition into compact state may be classified as a phase transition. Using equation of binding in Scetchard form one can obtain the theoretical dependencies of binding degree on the free ion concentration in solution at different values of the binding constant and cooperativity parameter. Comparing of theoretical curves with experiment permit us to estimate the binding constants and parameter of cooperativity for metal ion binding to DNA. Mixed solutions contained ethanol or glycerol change the cooperative parameter and binding constant. This effect is different for ethanol and glycerol and depends on the alcohol concentration.

5.13 Hierarchical Methods in Structure Calculations of Large Biomolecules

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The classical method of force field calculations requires minimizing the molecular energy as a function of the Cartesian coordinates of all atoms. Due to numerical problems caused by the large number of variables this method is limited to relatively small molecules of up to about 1000 atoms. To overcome this difficulty, the number of free variables is effectively reduced by assembling certain groups of atoms into configurational structures with considerably less degrees of freedom. In this way we build up a whole hierarchy of coordinate spaces with decreasing dimensions.

In addition, the energy function depending on the relative position of molecular subunits in space is approximated in hierarchically organized function spaces. Wavelets are used to describe the interaction energy of neighbouring atom groups. For approximation on Euclidean spaces we use cubic B-spline wavelets, whereas tensor products of B-spline wavelets and wavelets on an interval are appropriate for local approximation on SO(3). As an example we characterize the expansion in a wavelet basis of adenin-adenin interactions on a fine parameter grid. The resulting coefficient sequences are compressed using data compression techniques from the theory of image processing.

We also develop function expansions on SO(3). Convergence experiments show that positive definite functions are appropriate for the approximation of group energy functions if the distance of the groups exceeds five base pairs in the case of DNA. Therefore, PD-functions can be used to approximate long range interactions. On Euclidean spaces, also polynomial radial basis functions are candidates as well as multipole expansions.

We show applications of our hierarchical methods to theoretical model building studies of bulged DNA molecules like A1 to A9 bulged oligonucleotides.

5.14 Monte Carlo Methods for Polymer Modelling

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The correctness of the widely accepted statement that Molecular Dynamics (MD) is far more efficient in exploring the conformational space of macromolecules than Monte Carlo (MC) strongly depends on the choice of the MC move set. This is demonstrated for a number of molecular systems where MC (using a variety of move sets) and conventional MD are compared. Further applications of MC in structure prediction and determination of thermodynamical averages are presented.

5.15 The MaxFlux Algorithm for Calculating Variationally Optimized Reaction Paths for Conformational Transitions in Many Body Systems

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An algorithm for the calculation of reaction paths between known reactant and product states is described. The reaction path is defined as the path of maximum flux for a diffusive dynamics assuming isotropic friction. The resulting reaction path is temperature dependent and independent of the magnitude of the friction. Comparison is made with a number of algorithms designed for the calculation of minimum-energy reaction paths. Application to two model potentials and an extended atom model of a dipeptide demonstrates the ability of the algorithm to isolate reaction path on multidimensional molecular potential energy surfaces.

5.16 Free Energy Simulations of Oxidative Damage to Calmodulin

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Free energy simulations of oxidation process involving changes of methionine to sulfoxide (Met $\rightarrow$ Met*) at positions 144 and 145 are performed for the several states of calmodulin: without calcium (CAM), with bound calcium (CAM_2) and with bound calcium and target peptide (CAM_2:pep). The standard procedure for "alchemical" mutation of the normal Met sidechain to the oxidized sulfoxide from Met* is followed. The difference $\Delta\Delta G_{ca\ binding}$ between calcium affinity of the normal $\Delta G_{ca\ binding}$ and oxidized $\Delta G^*_{ca\ binding}$ forms. $\Delta\Delta G_{ca\ binding} = \Delta G^*_{ca\ binding} - \Delta G_{ca\ binding} = [G^*(\mathrm{CAM}_2) - G^*(\mathrm{CAM})] - [G(\mathrm{CAM}_2) - G(\mathrm{CAM})]$. Using the standard thermodynamic cycle approach we calculate these quantities as difference of introducing point mutations (Met $\rightarrow$ Met*) in the corresponding states: $\Delta\Delta G_{ca\ binding} = \Delta G_{mut}(\mathrm{CAM}_2) - \Delta G_{mut}(\mathrm{CAM})$. The simulation results have indicated the influence of oxidation on calcium and peptide binding.

5.17 Electrostatics of Biopolymers. A Finite Element Approach to a Poisson-Boltzmann Model

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Biomolecular structure and dynamics is to large extend determined by electrostatic interactions. In particular these interactions are involved in molecular recognition processes. In practical applications a mezoscopic Poisson- Boltzmann (PB) model is used for modelling electrostatic fields and forces, see e.g. [1,2]. In most cases a finite difference method, with fixed grids was used in biomolecular studies. The purpose of this approach is to formulate a computational model based on a finite element method, which is supposed to give a better accuracy, in particular for biomolecules with a complicated shape.
The Poisson-Boltzmann equation exhibits two types of singularities: the point charges contributing to the solution discontinuities at atoms, and surface discontinuities, both in terms of the dielectric constant and a nonlinear term.
It is therefore natural to apply the finite element method to a numerical solution of the PB equation. The authors use a triangulation of variable density controlled by the molecular geometry and containing the molecular surface as a subtriangulation. Initial runs have shown a very good numerical properties and speed of the algorithm applied. Test results for DNA molecules will be presented.

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[2] B.Lesyng and J.A.McCammon, Molecular Modeling Methods. Basic Techniques and Challenging Problems, Pharmac. Ther., 60, 149-167 (1993)

5.18 A Symplectic Method for Rigid-Body Molecular Simulation

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Rigid body MD simulations typically are performed in a quaternion representation. The nonseparable form of the Hamiltonian in quaternions prevents the use of a standard leap-frog (Verlet) integrator, so nonsymplectic Runge-Kutta, multistep or extrapolation methods are generally used. This is unfortunate since symplectic methods like Verlet exhibit superior energy conservation in long time integrations. In this article, we describe an alternative method, RSHAKE, in which the entire rotation matrix is evolved (using the scheme of McLachlan and Scovel [J. Nonlin. Sci., **16** 233 (1995)]) in tandem with the particle positions. We employ a fast approximate Newton solver to preserve the orthogonality of the rotation matrix. We test our method on a system of soft-sphere dipoles and compare with quaternion evolution using a 4th-order predictor-corrector integrator. Although the short-time error of the quaternion algorithm is smaller for fixed time step than that for RSHAKE, the quaternion scheme exhibits an energy drift which is not observed in simulations with RSHAKE, hence a fixed energy tolerance can be achieved by using a larger time step. The superiority of RSHAKE increases with system size.

5.19 New Fast Algorithm for Lattice Simulations of Polymer Systems

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The method of Monte Carlo simulation of polymer chains presented here bases on the simultaneous motion of a whole portion of the chain containing several beads in one time step. Such procedure is faster than obtaining the new conformation of the chain by gradual changing the conformation of a small fragment of the chain employing a set of elementary motions involving

one or two beads only. The presented examples of simulations show that our method gives correct results obtained in the shorter CPU time comparing with other techniques.

5.20 The Collisional Dynamics Method for Molecular Dynamics Simulations

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The collisional dynamics (CD) method is described. The CD method provides a natural mechanism of both energy and impulse exchange between the considered molecular system and its environment (a solvent). In the CD method stochastic collisions with virtual particles are included in the usual MD simulations to couple the studied system to the solvent. A comparison between the CD method and other well known methods, which treat solvent implicitly, is performed. The CD method seems to be more accurate in mimicing the dynamical properties of the studied system, especially in the non-equilibrium and time-dependent situations. Two examples of the use of the CD method in MD simulations are outlined. The first example concerns the study of the structural and dynamical properties of the iron-suphur cluster Fe4S4(SH)4 in protein environment. The second one presents the results of CD simulations of a polymer chain in a pulsating elongational flow.

5.21 Calculation of Effective Interaction Potentials From Radial Distribution Functions. Applications to Macromolecular Systems

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Despite of the fact that computers are becoming faster and faster each year, it will only be practical to simulate systems consisting of $10^3 - 10^4$ particles during a few hundred picoseconds in the near future. Simulations of complex biomolecules and their ionic environment in solutions involve much higher numbers of atoms, and one have to use simplified models in order to compromise. For example, to use continuum solvent model and hydrated ions. By now the primitive electrolyte model potential $1/\varepsilon r$ is often used for simulations of ions in solutions, but of course it is a rather crude approximation, especially on small distances between the ions.
Recently the new formulation of the reverse Monte Carlo method was suggested which provides reconstruction of interaction potentials from known radial distribution functions (RDF) [1]. One can prove that for any set of RDF there is a single set of pairwise effective potentials which reproduces this set of RDF. The suggested algorithm allows to find this set of potentials and so provides new perspectives for construction of effective potentials for simplified models. The general scheme is the following: simulation of a detailed system on low (full-atomic) level yield RDF which are used to derive effective potentials for simplified (continuum dielectric) models.
We have carried out molecular dynamics simulations of one turn of full-atomic model of DNA (CHARMM force field) in flexible-SPC water with Na^+ and Cl^- ions, and calculated the RDF-s between the ions and the phosphate groups on DNA. Then the reverse Monte Carlo procedure was applied which resulted in a set of effective potentials between the ions and between the ions and DNA. This set of potentials was then used to study ionic environment of DNA using the standard Monte Carlo algorithm in considerably larger simulation cell comparing to the original MD simulations. A simulation of a polyelectrolyte system using effective potentials consumes about equal computer time as a simulation using the primitive model. However the effective potentials reproduce structural properties (RDF) corresponding to the full account of the solvent on the molecular level.

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5.22 MD Simulation of Carbosile Dendrimers

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Dendrimers constitute a special class of regular branched polymers with unique physical and chemical properties which have attracted considerable attention recently. Description of their chemical structure is simple enough and consists of some standard elements: initiator core, repeat units, and terminal groups. It is special problem to obtain the dendrimer of sufficiently large size because as the number of atoms increases exponentially with the increase of diameter. That is why the building up the suitable initial structure for MD simulations is connected with considerable algorithmic difficulties when molecular weight of molecules is large.
In our calculations we use two ways (methods): (i) combined procedure which include a generation of consequent layer following by MD relaxation and (ii) creating "baobab" structures with the subsequent stepwise relaxation. During this calculation the special restraint and force fields were imposed on the system. We will cite results of MD simulations for carbosilane dendrimers of different topology and size. Particularly, the effect of initial structure on such characteristics of macromolecules as their shape, density distribution, and molecular mobility have been studied.

5.23 Protein Docking with Correlation Methods

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Hydrogen bonding and molecular surface shape complementarity may be used as a basis for the fast docking of proteins.
The components of a complex are represented on a 3D-grid for the structure prediction [1,2]. We use van der Waals radii for each atom if hydrogen atom coordinates are given and a united atom model is available for amino acids, nucleotides and some co-factors if hydrogen atoms are missing. The translation of the components and the scoring of potential complex structures is carried out with correlation techniques. The rotations of one component are monitored by linear combinations of Euler angles leading to an equally spaced sampling.
We have carried out docking simulations for 50 complexes. In most cases the highest correlation corresponds to the correct relative orientation. The error of the predicted coordinates is in the order of 1 A.
A search of complementary donor and acceptor atoms at the protein surfaces can be used as a filter to reduce the number of steps in the rotational search.

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5.24 Perturbation of Secondary Structure of Small Peptides by n-Alkylated Amino Acids: A Theoretical Study

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Previously presented calculations on the basic units of peptoid structures were completed by quantum chemical calculations and molecular dynamics simulations on model β turns with N-methylated glycine residues. The essential advantage of these compounds is there proteolytic stability at the substituted peptide bonds. Conformational preferences and energetic relations between various β turn subtypes were examined taking the βVI turn formation with *cis* peptide bonds into special consideration.

5.25 Local Interactions of Proline and Aromatic Residues in Short Peptides in Aqueous Solution: Database and Energetic Analysis Combine with Experimental Measurements

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Background: Although short peptides are usually structurally disordered in aqueous solution, particular peptide sequences can display local structures. Here, we studied one local interaction detected by 1H-nmr in a three residues peptide, APY(i), excised from bovine pancreatic trypsin inhibitor: (i-1)cisproline-aromatic. Previous studies have analyzed the case of a competitive interaction: aromatic-(i+2)amide. To obtain an atomic detail description of these interactions, we performed database and conformational searches along with molecular dynamics simulations.
Results: The calculations show that there are at least two major and distinct peptide conformations in the folded state. The ring packs either on to the (i-2)CaH or the (i-1)CgH. The energy barrier between the two conformations is about 35kJ/mol. And the computed proton chemical shifts are compatible with the experimental ones.
Conclusions: These local aromatic interactions may arise as the result of different combinations of inter-atomic interactions. Although weak, they can influence folding and binding properties.

5.26 Molecular Dynamic Simulation of Regular Polymer Networks

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Algorithm for the construction and simulation of molecular motion of the regular polymer network has been developed. Both NPT and NVT ensembles can be used. Local structural and dynamical properties were calculated at different values of density and strand length. Effect of crosslinks on the intrachain mobility was studied.

5.27 Essential Dynamics of Mutated DNA

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The Essential Dynamics technique [1] can be used to find functional relevant motions in proteins. Here this techniques will be used to find the characteristic motions in a molecular dynamics simulation of a 8-OXO-guanine mutated DNA sequence.

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5.28 Use of Mean-Force Potentials for Protein Structure Prediction

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We have investigated the use of mean-force potentials (MFPs) for predicting protein tertiary structure. As a simple test case, we chose to work with leucine zippers (LZs) for which accurate 3D prediction from the sequence alone is already possible using all-atom molecular dynamics (Nilges & Brunger, 1993) and other methods. The backbone coordinates of LZs can be described using the coiled coil equations, first derived by Crick in 1952. Assuming the standard α-helical parameters, the coiled coil equations have just three free parameters. Using the mean-force potential proposed by Sippl (1990), we have developed an exhaustive grid search strategy for finding the optimal coiled coil parameters for a given sequence. The method was applied to three LZs: the homodimers of GCN4 and Jun, and the Jun-Fos heterodimer. In each case, the search produced a lowest-energy structure within about 1$\mathring{A}$ RMSD from the experimentally determined structure. Three main conclusions can be drawn from these results. Firstly, the results show that, at least for one class of folds, MFPs can be used to accurately predict protein structure. Secondly, the MFPs appear to successfully describe intermolecular interactions even through these potentials were derived from a subset of the PDB from which multimers were excluded. Thirdly, as a method for predicting the 3D structure of LZs, our method achieves the same or better accuracy as previously all-atoms based methods, and is much faster.

5.29 Structure-Preserving Algorithms for Dynamical Systems

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It is well know, that Dynamical systems are the mathematical equations for the research modern's mechanics, physics, Chemistry biology and even for the laws of the developments of social sciences. Besides the analytic method for studying the behavior of them, numerical method is an indispensable instrument. Most of the Dynamical systems in sciences and engineering are nonlinear, they have essential distinctions with the linear systems. The research of Dynamical systems is highly complex. The developments of modern computers provide a powerful instrument which makes new progress take place in the research of Dynamical systems. A basic but unwritten rule for the research on numerical methods is that the properties of the original problem should be preserved as much as possible under discretization. The best way to achieve this aim is to work out the analog within the same framework of the original. For example, the symplectic geometry is the mathematical framework of Hamiltonian system. So Dynamical algorithm for Hamiltonian system should be originated from within the framework of symplectic geometry i.e. best algorithm for them should be preserving symplectic structure. Since Feng Kang proposed symplectic algorithms for Hamiltonian systems, numerical methods for Dynamical systems have been systematically developed. These numerical methods possess the property of structure-preserving, which means the preservation of symplectic structure for Hamiltonian systems, the preservation of volume for source-free systems and the preservation of

contact structure for contact systems. These methods are often referred to as geometrization of algorithms related to symplectic, volume-preserving and contact geometry.
In this paper, we consider the Dynamical system in R^n

$$\frac{dx}{dt} = a(x)$$

defined by a vector field $a(x)$. where $a(x)$ may be hamiltonian, source free, or contact vector field. We constructed for them symplectic, volume, contact integrators respectively.

5.30 Monte Carlo Simulations of Chain Molecules: Application of the Continuum Model to Intramolecular Bond Ordering

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Monte Carlo procedure for computer simulation of the conformational behaviour of chain molecules with a predetermined chemical structure (continuum model) is proposed. Variations of all bond rotation angles of the chain were considered to be continuous from 0 to 360 deg in contrast to the RIS scheme. A mathematical technique of the importance sampling of molecule conformations is developed. The method is applied to an investigation of intramolecular bond ordering of hydrocarbon chains (N=18-22) with 1-6 double bonds (typical components of nature lipids). The molecule-fixed coordinate system (with the axes along principal axes of inertia of each molecule conformation) has been used.
The orientation distribution functions R(A) of C-H and C-C bonds, order parameters S relative to the maximum molecule span axis have been calculated (A is the angle between the bond and the axis). The relation of the bond orientation distributions R(A) to the order parameters S are analyzed in terms of angles Amax (the geometric factor, R(Amax) = max) and widths DA of the distributions (factor of fluctuations).
The widths DA turned out to be dependent on the segment chemical structure and position; fluctuations increase from the centre of the chain towards the terminals, all things being equal. The functions R(A) of C-H bonds flanking the double bond are the most narrow, the functions R(A) of methylene groups located between two double bonds are the most wide. The two DA values of C-H bonds flanking the double bond are smaller than that obtained for adjacent methylene groups by a factor of 1.5 - 2.
The double bond parameters Scc is found to be more high than those of adjacent single C-C bonds. The parameter Scc odd-even effect in the unsaturated molecules of such structure changes sign between double bonds. The mean molecule magnitudes of S of C-H bonds decrease when unsaturation increases. Some other properties of the molecules are discussed.
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5.31 Extrapolation of Hydration Free Energies

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Hydration free energies of a number of small organic molecules are calculated from a single simulation of a reference state. To enhance sampling at this reference state we used cavities with a soft core potential that varied in the height of the barrier. The perturbation formula was used to calculate the free energy differences. 3 KbT turned out to be a suitable barrier height which gave the highest accuracy. The resulting hydration free energies were compared to data from Thermodynaimc Integration and experiment.

5.32 MD-Simulation of Polyethylene/Polypropylene Interfaces

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Computer simulation of HDPE (high density polyethylene) and iPP (isotactic polypropylene) interfaces: it was supposed that epitaxial interfaces which could be observed in sandwiched films of PE and iPP are responsible for increased impact strength of iPP and HDPE blends. Since it is not possible to investigate the interfacial region experimentally, computer simulation was performed. Interfaces of HDPE and iPP - amorphous/crystalline, amorphous/amorphous and crystalline/crystalline (a-modification of crystalline iPP), has been investigated over 0.5 ns of atomistic molecular dynamic simulation. Adhesion energies of different types of crystalline/crystalline interfaces were compared in order to find the most stable interface.

5.33 Simulations of a Surfactant Micelle Using a Polarizable Model

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The structure and electrostatics of the interface of aqueous sodium octanoate micelles have been studied using molecular dynamics simulations employing nonpolarizable and polarizable models. We find that the hydrocarbon/water interface is only about 4 wide and that there is a distinct electric double layer. The collective nature of dielectric screening is apparent. Significant cancellation occurs between the relatively large contributions to the electrostatic potential, resulting in a relatively small net electrostatic potential. Simulations employing our polarizable models give only a few Na+ ions in contact with the carboxylate headgroups, in closer agreement with experiment than our nonpolarizable models.

5.34 Ab-initio Molecular Dynamics Simulations of Chemical Processes in Macromolecular Environments

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Ab-initio Molecular Dynamics simulations schemes are examined for use in propagation of nuclear and electronic degrees of freedom in simulations of proton transfer processes in macromolecular environments. Implementation of a scheme with localized basis functions for the massively parallel T3D at Zuse Zentrum and general performance of the method are discussed. Applications of ab-initio Molecular Dynamics simulation to cluster in a macromolecular environment are presented.

5.35 Conformational Properties of Peptides with Dehydroamino Acids

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On the basis of high-level *ab initio* MO quantum-chemical calculations (MP2/6 − 31G*, HF/6 − 31G*, solvation effects) and molecular dynamics simulations, the conformational structure possibilities of peptides containing various types of dehydroamino acids are systematically examined. In particular, the influence of conjugation and stereochemical effects (Z and E configuration) on the structure was subject of a detailed study. There is a characteristic conformation pattern which is also reflected in typical tendencies for secondary structure formation as shown for β turns.

5.36 Modeling of the Plastocyanin-Cytochrome f-Complex. Simulations and Calculations of Electron-Transfer Pathways

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In this poster, we present a theoretical analysis in four stages of association between the blue copper protein plastocyanin and the heme protein cytochrome f, which are physiological partners in the photosynthetic electron-transfer chain. In the first stage, several Monte Carlo trajectories of approach by plastocyanin to cytochrome f were generated. The molecular configurations having relatively low energies were grouped, by structural similarity, into six families. In the second stage, six configurations having the lowest energies, one from each family, were subjected to thorough molecular dynamics simulation, for 260 ps. Extensive hydration of the proteins was treated explicitly. The whole plastocyanin molecule and the relevant parts of the cytochrome f molecule were given conformational freedom. In the third stage, the following three contributions to the energy of binding were calculated: polarization of water by the proteins, determined from numerical solutions of the Poisson-Boltzmann equation; nonelectrostatic (van der Waals and other) interactions involving the proteins and water; and the coulombic interactions within and between the protein molecules. Total energy of association was calculated with a thermodynamic cycle; several realistic sets of parameters gave consistent results. The configuration having the most favorable coulombic interactions turned out to have the second highest total energy. This finding exemplifies the importance of allowing for hydration and for conformational flexibility in docking calculations and perils of neglecting these factors. In the fourth stage, electronic coupling between the copper and heme sites in the six configurations was analyzed and compared by the *Pathways* method. The configuration providing the most efficient path for electron tunneling turned out to be different from the most stable configuration. There are indications that the evident interaction between Lys65 in cytochrome f and Tyr83 in plastocyanin may involve the ammonium group of the former and the aromatic ring of the latter. These surprisingly strong noncovalent interactions, so-called charge-π interactions, have recently been discovered and are important for molecular recognition. Modeling and structural optimization of these interactions are beyond the state of the art in molecular mechanics, but these studies should become possible with improved force fields. The electron-transfer reaction between cupriplastocyanin and ferrocytochrome f is fast in the noncovalent complex and undetectably slow in the covalent complex. This contrast is explained in terms of our theoretical analysis.

5.37 A Molecular Dynamics/Potential Annealing Approach to Build Amino Acid Side Chain Coordinates on a Semi-Flexible Protein Main Chain

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The prediction of amino acid side chain coordinates is an important step in the homology building of proteins with sequence similarity to proteins with known X-ray structure. A number of methods is available to generate full protein coordinates from a limited set of protein main chain coordinates based on rules obtained from a set of known protein structures or through sequential addition of side chain atoms combined with energy minimization and molecular dynamics. In the present study, a potential annealing approach based on the separation-shifted scaling for Lennard-Jones interactions (Zacharias et al., J.Chem.Phys. 100, 9025) has been used to obtain side chain coordinates during a molecular dynamics simulation.
Starting from random placements of the side chain atoms the Lennard-Jones potential of the side chain atoms is slowly grown from nothing to the full potential in the course of the simulation. The protein main chain atoms are restrained to the X-ray or NMR coordinates of the known reference structure. Modifications of the basic approach like a two copy representation of side chains and using a side chain torsion angle potential of mean force based on the side chain rotamer distribution in known protein structures have also been tested. For some test cases the prediction accuracy expressed as rms-(root-mean-square) deviation from the observed side chain placement is smaller than 1.5 A for most residues in the protein interior. This is comparable to existing methods with fixed main chain coordinates. In contrast, the present approach allows for some readjustment of the main chain coordinates during the side chain building process. This might be an advantage in cases of weak sequence similarity between the known and homologous structures where correct side chain placement without main chain readjustment might be difficult.

5.38 Quantum Dynamics of HCl Photodissociation in Ar_{12} Cluster

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The hydrogen atom quantum dynamics following HCl photodissociation in argon environment is studied using the classical based separable potential method with spherical harmonic expansion of the solute rotational motions.

5.39 Large Scale Simulations of Solvated Proteins: Combining a Multiple Time Step Integrator with a Periodic Fast Multipole Method

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Large scale simulations of macromolecules in solution that do not suffer from artifacts arising from force truncations are becoming feasible. New force evaluation algorithms such as the Fast Multipole Method (FMM), and multiple time scale integration methods such as the reversible Reference System Propagator Algorithm (r-RESPA) have been combined and used to perform fast and stable simulations of large macromolecular systems. A consistent treatment of the long-range forces in simulations with periodic boundary conditions requires the use of a periodic form of the Coulomb potential. In this paper, the FMM is extended to periodic systems with a full derivation of the local field expansion from distant replica multipoles. The periodic FMM is then combined with RESPA, yielding a new algorithm that is successfully applied to the simulation of large biomolecules in solution. If the interactions at different stages are separated smoothly, good energy conservation is obtained even for time steps as large as 12 fs on a system of over 40,000 atoms, and a CPU speedup of more than a factor of 20 is achieved compared to the standard Verlet integrator with Ewald sum for the Coulombic interaction. As compared

with the recently developed particle-mesh Ewald (PME) method, the periodic r-RESPA/FMM has a break-even point at about 20,000 atoms; for larger systems, r-RESPA/FMM is expected to be more efficient.

5.40 Study of Classical Trajectory of the H_2O in Chemical Reaction Dynamics

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Classical Trajectory of H_2O have been calculated by using both symplectic and Runge-Kutta algorithms, and the comparison between the results of the two are illustrated. It is shown that within the whole domain of time that shold be considered by micro chemical reaction dynamics, the energy and the trajectory of H_2O computed by using symplectic algorithm are always identical with physical analysis. However, those by using Runge-Kutta's are irregular and unpredictable. Moreover, computation of classical trajectory by symplectic algorithm instead of traditional numerical algorithms may critically improved classical trajectory method in chemical reaction dynamics.

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