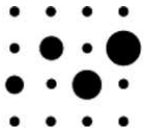

VolkswagenStiftung

Heidelberg University

Workshop on computer simulations of soft matter and biosystems

March 14 – 16 2007

Heidelberg University

Kirchhoff Institute for Physics (KIP)

Im Neuenheimer Feld 227

1 General information

1.1 Aim

This workshop (`www.bioquant.uni-heidelberg.de/workshop2007`) is part of the first call of the funding initiative of the Volkswagen Foundation on "New conceptional approaches to model and simulate complex systems", which was concerned with computer simulation of molecular and cellular biosystems as well as complex soft matter. It provides a forum for the funded projects to present their results, to discuss current issues of interests and to develop new perspectives for future research.

1.2 The Volkswagen Foundation

The Volkswagen Foundation (`www.volkswagen-stiftung.de`) is a non-profit-making foundation established under private law based in Hanover. Its objective is to support science, the humanities and technology in research and higher education. It funds research projects in path-breaking areas and provides assistance to academic institutions for the improvement of the structural conditions for their work. In particular, the Foundation perceives its mission in supporting aspiring young academics and in promoting interdisciplinary and international collaboration. The Foundation owes its existence to a treaty between the Governments of the Federal Republic of Germany and the State of Lower Saxony, which settled a controversy over the ownership of the Volkswagen factories after 1945. As a result the Foundation was set up in 1961; it is not affiliated to the car manufacturer of the same name. It is economically independent and autonomous in its decision-making. At present the Foundation's assets amount to 2.4 billion euros. Since its beginnings the Foundation has supported about 28,400 different projects, providing funding to the tune of some 3.3 billion euros. On average it allocates about 100 million euros of funding per year.

1.3 Heidelberg University

At Heidelberg University (`www.uni-heidelberg.de`), a large research effort is on its way for modelling and simulation of biological system, in close collaboration between the natural and life sciences. This effort includes the following initiatives:

- **BIOQUANT** (`www.bioquant.uni-heidelberg.de`), a large research network for quantitative biology focused around a new building in the Neuenheimer Feld which is going into operating in March/April 2007.
- **BIOMS** (`www.bioms.de`), the Center for Modelling and Simulation in the Biosciences, comprises three junior research groups (Francois Nedelec, Ulrich Schwarz and Matthias Weiss) as well as a Postdoc and guest programs
- **VIROQUANT** (`www.viroquant.uni-hd.de`), one of four new centers for systems biology in Germany funded by the Federal Ministry of Education and Research (BMBF), aims at a systematic understanding of host-virus interactions

- **CellNetworks** (`www.cellnetworks.uni-hd.de`), the first cluster of excellence at Heidelberg University, concerns itself with a complete and quantitative understanding of cellular networks in health and disease

1.4 Organization

Scientific Organization

Francois Nedelec, EMBL Heidelberg
Karsten Rippe, KIP, Heidelberg University
Ulrich Schwarz, BIOMS, Heidelberg University
Jeremy C. Smith, IWR, Heidelberg University

General Organization

Ulrike Bischler, Volkswagen Foundation
Herta Fitzer, BIOMS, Heidelberg University
Jakob Schluttig, BIOMS, Heidelberg University
Ulrich Schwarz, BIOMS, Heidelberg University

1.5 Venue

The "Kirchhoff Institute for Physics" (KIP, Im Neuenheimer Feld 227, 69120 Heidelberg) was officially founded in November 1999 with the merging of the existing "Institut für Angewandte Physik" (IAP) and the "Institut für Hochenergiephysik" (IHEP). In 2002 the institute moved into the new building in the Neuenheimer Feld. The institute is dedicated to research and teaching in the areas of physics and computer science. It is located in the center of the university campus "Im Neuenheimer Feld", in close vicinity to the new BIOQUANT-building.

1.6 Contact

Jakob Schluttig
Center for Modelling and Simulation in the Biosciences (BIOMS)
Ruprecht-Karls-University Heidelberg
Im Neuenheimer Feld 293 (URZ)
D-69120 Heidelberg, Germany

Phone: +49-(0)6221-54-4993
Fax: +49-(0)6221-54-8652
Email: Jakob (dot) Schluttig (at) iwr (dot) uni-heidelberg (dot) de
Internet: http://www.bioms.de/schwarz

1.7 Program

Wednesday, March 14th

12.00 – 13.30	**ARRIVAL MEAL**
13.30 – 14.00	**PD Ulrich Schwarz, Dr. Indra Willms-Hoff, Prof. Willi Jäger** Welcome
14.00 – 15.00	**Prof. Alan Mark** Self-assembly of Peptides and Membranes
15.00 – 15.30	**Prof. Helmut Grubmüller** Collective motions of biological macromolecules
15.30 – 16.00	**Dr. Kei Moritsugu** Langevin Model of Protein Dynamics
16.00 – 16.30	**COFFEE**
16.30 – 17.00	**Prof. Martin Zacharias** Nucleic acid and peptide conformation studied by molecular dynamics and advanced sampling methods
17.00 – 17.30	**Dr. Nick Kepper** Modeling Chromatin Fibers I: Effect of Nucleosome Geometry
17.30 – 18.00	**Prof. Gero Wedemann** Modeling chromatin fibers 2: effects of interactions between nucleosomes
18.00 – 18.30	**Jakob Schluttig** Modelling large protein clusters
18.30 – 19.00	**Poster Introductions**
19.00	**Postersession + DINNER**

Thursday, March 15th

09.00 – 10.00	**Prof. Wilfred van Gunsteren** Methods to simulate biomolecular systems
10.00 – 10.30	**Prof. Walter Thiel** Correlated ab initio QM/MM studies of enzymes
10.30 – 11.00	**Prof. Reinhold Fink** New ab initio multi configuration approaches designed for QM/MM applications
11.00 – 11.30	**COFFEE**
11.30 – 12.00	**PD Nikos Doltsinis** Photoisomerisation in liquid azobenzene studied by nonadiabatic QM/MM simulations
12.00 – 12.30	**Dr. Christine Peter** Classical simulations from the atomistic to the mesoscale: coarse-graining an azobenzene containing liquid crystal
12.30 – 14.00	**LUNCH**
14.00 – 15.00	**Prof. Gerhard Gompper** Soft Matter Hydrodynamics
15.00 – 15.30	**Jens Smiatek and Ulf D. Schiller** A new way of implementing partial slip boundary conditions
15.30 – 16.00	**Kai Grass** Electrohydrodynamics in bulk and in confined geometries
16.00 – 16.30	**COFFEE**
16.30 – 17.00	**Dr. Anthony Maggs** Aspects of fluctuation potentials in dielectrics
17.00 – 17.30	**PD Dirk Hennig** Cooperative escape dynamics of nonlinear oscillator chains
17.30 – 18.00	**Dr. Ilona D. Kosinska** Transport in nanopores
19.00	**DINNER Kulturbrauerei Heidelberg** `www.heidelberger-kulturbrauerei.de`

Friday, March 16th

09.00 – 10.00	**Prof. Jeremy Smith** Dynamics of Protein Binding, Reaction and Structural Change
10.00 – 10.30	**Dr. Francois Nedelec** Modelling Microtubules Structures
10.30 – 11.00	**Dr. Alexey Zaikin** Proteamalg: a new tool for in vitro digestion assay performed by 20S immunoprotasome and PA28
11.00 – 11.30	**COFFEE**
11.30 – 12.00	**Dr. Esa Kuusela** Cytoplasm and integrin dynamics in a 2D continuum model for cell migration
12.00 – 12.30	**Dr. Björn Nadrowski** The physics of an ear
12.30 – 13.00	**Dr. Ulrike Bischler, PD Ulrich Schwarz** Closing remarks

1.8 Posters

Denitsa Alamanova, Ines Hörger, Volkhard Helms
Brownian dynamics simulations on a lattice

Benedix, de Groot, Caflisch, Böckmann
CONCOORD/PBSA: A Versatile Method for the Prediction of Mutant Free Energy & Structure

Marcus Böckmann, Nikos Doltsinis, Dominik Marx
Probing the Photoswitch: Hybrid QM/MM AIMD Studies on Liquid Azobenzene

Manfred Bohn and Dieter W. Heermann
Chromosomes on Small and Large Scales

Jeremy Curuksu, Krystyna Zakrzewska, Martin Zacharias
Advanced Molecular Dynamics and Umbrella Sampling of DNA bending and backbone dynamics

R. Fink, W. Thiel, B. Engels
QM/MM Characterisation of irreversible Inhibitors

Gernot Guigas, Matthias Weiss
Size-dependent diffusion of membrane inclusions and non-equilibrium fluctuations of lipid bilayers as studied by mesoscopic simulations

Rafael Gutierrez, Dmitry Ryndyk, Bo Song, and Gianaurelio Cuniberti
Conductance Properties of DNA molecular wires

Christoph Junghans, Michael Bachmann, Wolfhard Janke
Microcanonical analysis of polymer aggregation

U. Kleinekathöfer, S. Pezeshki. C. Chimerel, M. Winterhalter
Simulation of transport through OmpF channels

Christian B. Korn and Ulrich S. Schwarz
Probability for specific bond formation for a Brownian particle in linear shear flow above a wall

G. Kreth, J. Odenheimer, D.W. Heermann
Dynamic simulation of active and inactive chromatin domains

Marcus B Kubitzki and Bert L. de Groot
Molecular Dynamics Simulations using Temperature Enhanced Essential dynamics Replica EXchange (TEE-REX)

OF Lange and H Grubmueller
Collective Langevin Dynamics of Conformational Motions in Proteins

Jörg Langowski
DNA dynamics on the nucleosome simulated by coarse-grained models

David Minde
Designed Flexible Fusogenic Transmembrane Domains in TFE

M. Mosayebi, M. Reza Ejtehadi
Significance of native state contact map topology in protein folding dynamics

Daniele Narzi and Rainer Böckmann
Dynamic Protonation State Analysis of Dsb Proteins

Georgi V. Pachov, Rebecca C. Wade
Simulation of linker histone in chromatin fiber

Igor Pasichnyk, Ralf Everaers
Simulating van der Waals-interactions in water/hydrocarbon-based complex fluids

M. Praprotnik, L. Delle Site and K. Kremer
Adaptive Resolution Molecular Dynamics Simulation: Changing the degrees of freedom on the fly

Ellen Reister-Gottfried, Stefan M. Leitenberger, and Udo Seifert
Lateral diffusion of proteins in fluctuating membranes

Marcello Sega, Christian Holm
Simulating electroosmotic flow using Lattice Boltzmann technique

Srinivasaraghavan Kannan, Martin Zacharias
Exploring the Conformational Space of Biomolecules by Biasing Potential Replica Exchange Molecular Dynamics Simulations

A. Verma, S. M. Gopal and W. Wenzel
Towards a universal free energy forcefield for all atom protein folding

2 Abstracts – Keynote Lectures

Modelling self-organization in biomolecular systems: Simulating the folding and aggregation of peptides, proteins and lipids.

Alan E. Mark

School of Molecular and Microbial Sciences and the Institute for Molecular Biosciences, University of Queensland, St Lucia, 4072, Queensland, Australia
Lab. of Biophysical Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands. http://md.chem.rug.nl
eMail: a.e.mark@uq.edu.au
WWW: http://profiles.bacs.uq.edu.au/Alan.Mark

Computer simulations of proteins, lipids and nucleic acids at equilibrium have become essentially routine. The challenge for the future is to use such approaches to understand spontaneous selforganization in biomolecular systems (folding, aggregation and selfassembly of complexes), processes that cannot be directly observed experimentally. While it is not yet possible to fold complete proteins using atomic models, dramatic progress has been made regarding the folding and aggregation of peptides, the spontaneous selforganization of phospholipids into micelles and bilayers, and the assembly of peptides and proteins at interfaces. For example, the process by which phospholipids assemble into membranes can now be simulated in detail. The resulting membrane water interface provides, in turn, a powerful driving force to initiate the folding and selfassembly of peptides and proteins. A range of examples illustrating the extent to which simulations can be used to understand cooperative phenomena in biomolecular systems will be presented along with examples of where the methodology must still be developed further.

Methods to simulate biomolecular systems

Wilfred F. van Gunsteren

Laboratory of Physical Chemistry ETH - Swiss Federal Institute of Technology Zurich CH-8093 Zurich, Switzerland
eMail: wfvgn@igc.phys.chem.ethz.ch
WWW: http://www.igc.ethz.ch/

Computer simulation of the dynamics of biomolecular systems by the molecular dynamics (MD) technique yields the possibility of describing the structure-energy-function

relationships of molecular processes in terms of interactions at the atomic level. Important processes or thermodynamic equilibria are governed by weak (non-bonded) forces: polypeptide folding, biomolecular association, partitioning between solvents and membrane or micelle formation. When modelling these processes four problems must be addressed: the force field problem, the search problem, the ensemble problem and the experimental problem. These will be discussed, illustrated with examples and methodological advances to solve them will be shown.

[1] Wilfred F. van Gunsteren *et al.*, Angew. Chem. Int. Ed. **45**, 4064-4092 (2006)

Soft Matter Hydrodynamics

Gerhard Gompper

Theoretical Soft-Matter and Biophysics, Institut für Festkörperforschung, Forschungszentrum Jülich GmbH, 52425 Jülich, Germany
eMail: G.Gompper@fz-juelich.de
WWW: http://www.fz-juelich.de/iff/d_th2

The dynamics of soft matter systems – such as colloidal suspensions, dilute and semi-dilute polymer solutions, and vesicle dispersions – is often dominated by the hydrodynamic behavior of the solvent. For example, the flow properties of blood in micro-vessels is determined by the rheological properties of the red blood cells, and polymers unfold, tumble and collapse in shear flow. Furthermore, microfluidic devices have been developed recently, which allow the manipulation of small amounts of suspensions of particles or cells.

Due to the large length- and time-scale gap between the atomic and the mesoscopic domain in soft matter systems, several mesoscale simulation techniques have been developed in recent years to study their hydrodynamic behavior. We have investigated one of these techniques, multi-particle-collision dynamics, in some detail. In particular, it has been shown that the method properly describes hydrodynamic interactions at low Reynolds numbers, if the parameters are in an appropriate range [1].

This method has then be applied recently to study the dynamical behavior of fluid vesicles and model red blood cells both in shear and capillary flows [2,3,4], as well as of star polymers in shear flow [5].

[1] M. Ripoll, K. Mussawisade, R.G. Winkler and G. Gompper, Europhys. Lett. **68**, 106 (2004)
[2] H. Noguchi and G. Gompper, Phys. Rev. Lett. **93**, 258102 (2004)
[3] H. Noguchi and G. Gompper, Proc. Natl. Acad. Sci. USA **102**, 14159 (2005)
[4] H. Noguchi and G. Gompper, Phys. Rev. Lett. **98**, in press (2007)
[5] M. Ripoll, R.G. Winkler and G. Gompper, Phys. Rev. Lett. **96**, 188302 (2006)

Dynamics of Protein Binding, Reaction and Structural Change

Jeremy Smith

The Computational Molecular Biophysics Group, IWR, Uni-Heidelberg, INF 368, 69120 Heidelberg, Germany
eMail: biocomputing@iwr.uni-heidelberg.de
WWW: http://spider.iwr.uni-heidelberg.de/jsmith/

Computer simulation results on dynamical effects influencing ligand binding, reactions and the mechanics of large-scale conformational change in proteins will be discussed. Among the questions to be examined are the thermodynamic consequences of vibrational changes on ligand binding, the protein glass transition and function, proton transfer reactions in the light-driven proton pump protein, bacteriorhodopsin, and the mechanics of the power stroke of muscle contraction.

3 Abstracts – Talks

Langevin Model of Protein Dynamics

Kei Moritsugu and Jeremy C. Smith

Computational Molecular Biophysics, Interdisciplinary Center for Scientific Computing(IWR), University of Heidelberg, Im Neuenheimer Feld 368, 69120 Heidelberg
eMail: Kei.Moritsugu@iwr.uni-heidelberg.de

Molecular dynamics (MD) simulation is the most powerful computational tool to analyze protein dynamics and function at the atomic level. However, the available MD trajectories are limited in the timescale and the number of atoms due to expensive computational cost. For reproducing the protein motion on the biologically-relevant timescales, in this study, normal modes or principal component modes are applied to the MD trajectories to define the subspace describing slow functional motions in combination with simple dynamical models via the Langevin equation. The first model using the damped oscillator parameterized by the Langevin friction and the potential of mean force are shown to characterize the vibrational motion along each normal mode. The temperature dependence and solvent effect on protein dynamics are describable via these parameters. The extended model including both the Langevin vibration and simple diffusion is constructed for the anharmonic dynamics along the large-amplitude principal component mode. Using the modified model the dynamical transition phenomena of protein dynamics is clarified as the excitation of the diffusive motions at the transition temperature. The dynamic structure factor from the full molecular dynamics trajectory is well reproduced by the model, indicating that protein motions on long-timescale can be obtained by applying the present model to the subspace comprising of selected number of normal modes or principal component modes.

[1] Kei Moritsugu and Jeremy C. Smith, J. Phys. Chem. B **109**, 12182 (2005)
[2] Kei Moritsugu and Jeremy C. Smith, J. Phys. Chem. B **110**, 5807 (2006)

Nucleic acid and peptide conformation studied by molecular dynamics and advanced sampling methods

Martin Zacharias

International University Bremen / School of Engineering and Science, Campus Ring 1, D-28759 Bremen
eMail: m.zacharias@iu-bremen.de

In principle molecular dynamics (MD) simulations are ideally suited to study the fine structure and structural transitions in nucleic acids and proteins at very high spatial and time resolution. However, for many applications the currently accessible time scales of MD simulations are too short to sample all relevant conformational states or to simulate folding of structural motifs in nucleic acids or proteins. Replica-exchange MD (RexMD) simulations allow significantly improved sampling of conformational space and is increasingly being used to study peptides and proteins. However, so far very few applications to nucleic acids have been described. During RexMD simulations several replicas of a system are simulated at different temperatures in parallel allowing for exchange between replicas at frequent intervals. We have applied this method to successfully fold a stable DNA hairpin motif starting from an extended chain to final structures in very close agreement with experiment as the dominant state (in the lowest temperature replica). This was achieved in several independent explicit solvent RexMD simulations and allowed us to suggest a folding mechanism based on stable intermediates and mis-folded structures. A drawback of standard temperature RexMD is the rapid increase of the required number of replicas with increasing system size to cover a desired temperature range. In an effort to limit the number of replicas we have developed a new Hamiltonian-RexMD method that is specifically designed to enhance the sampling of peptides and proteins by applying various levels of a backbone biasing potential for each replica run. The biasing potential lowers the barrier for backbone dihedral transitions and promotes enhanced peptide backbone transitions along the replica coordinate. The biasing potential (BP)-RexMD method requires only a very modest number of replicas and was successfully tested on several peptide systems [1]. Efforts to use a similar methodology also for conformational sampling of nucleic acid structures will be discussed.

[1] Kannan S, Zacharias M, Proteins **66**, 697 (2007)

Monte Carlo simulations of chromatin fibers I: Effect of the nucleosome Geometry

Nick Kepper[1], Rene Stehr[2], Evrim Ilden[1], Dietrich Foethke[1,3], Gero Wedeman[2], and Karsten Rippe[1]

[1] Kirchhoff-Institut für Physik, Molecular Biophysics Group, Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 227, D-69120 Heidelberg, Germany
[2] Fachhochschule Stralsund, System Engineering and Information Management, Zur Schwedenschanze 15, D-18435 Stralsund, Germany
[3] present address: Cell Biology and Biophysics, European Molecular Biology Laboratory, Meyerhofstrasse 1, D-69117 Heidelberg, Germany
eMail: nikolaus.kepper@kip.uni-heidelberg.de
WWW: http://www.kip.uni-heidelberg.de/chromcon/

In the cell nucleus of eukaryotes the DNA is packaged by histone proteins into a chain of nucleosomes, in which 146 or 147 base pairs of DNA are wrapped in 1.67 turns of a left-handed superhelix around a octameric histone protein core. The resulting DNA linked of nucleosomes associates under physiological conditions into a highly condensed chromatin fiber with a diameter of about 30 nm. The conformation and dynamic properties of this 30 nm fiber are important factors for controling the access of the DNA with interacting protein factors involved in gene expression. Here, the effect of the DNA–nucleosome geometry on the conformation of chromatin fibers was studied by Force field, Molecular Dynamics (MD) and Monte Carlo (MC) simulations. We extended the previously proposed "two angle" model for the geometry of the DNA at the nucleosome by additional degrees of freedom. This allowed it to describe the trajectory of DNA entering and leaving the nucleosome in a more realistic manner so that conformations found in crystal structures, cryo-electron microscopy studies or those predicted from force field model building approaches could be reproduced. The results of our analysis identify the local DNA geometry at the nucleosomes as an important parameter for the organization of the chromatin fiber at physiological ionic strength. It is shown that small changes in the angles that determine the DNA paths lead to surprisingly large changes from a compacted fiber conformation and into an extended conformation. This transition might be related to the formation of a state where access to the DNA is facilitated for biological processes.

Monte Carlo simulations of chromatin fibers II: effects of interactions between nucleosomes

René Stehr[1], Nick Kepper[2], Karsten Rippe[2], Gero Wedemann[1]

[1]Institute for Applied Computer Science, Fachhochschule Stralsund, Zur Schwedenschanze 15, D-18435 Stralsund.
[2]Molecular Biophysics Group, Universität Heidelberg, Im Neuenheimer Feld 227, D-69120 Heidelberg
eMail: gero.wedemann@fh-stralsund.de
WWW: http://www.user.fh-stralsund.de/~gwede

The organization of the 30 nm chromatin fiber determines the DNA accessibility, and is therefore an important parameter for controlling gene expression. We have studied the effect of different interaction potentials between nucleosomes on the chromatin fiber conformation by Monte Carlo simulations. Three types of nucleosome shapes were investigated: A sphere modeled by a Lenard-Jones potential, an oblate ellipsoid modeled by a Gay–Berne potential and an oblate cylinder modeled by a new developed potential. In the latter the strength and distance parameters of the shifted Lenard–Jones potential were replaced by anisotropic S–functions in similar manner as in the Gay-Berne potential. The analysis revealed that the spherical or ellipsoid potentials are not compatible with the formation of stable chromatin fibers if the experimentally determined values of 1–2 kT for the interaction strength between nucleosomes are used. Only the cylindrical shaped nucleosome potential was found to be in agreement with the experimental data on the stability of chromatin fibers.

Modelling large protein clusters

Jakob Schluttig, Ulrich Schwarz, Denitsa Alamanova, Ines Hörger, Volkhard Helms

Center for Modelling and Simulation in the Biosciences (BIOMS), Ruprecht-Karls-University Heidelberg, Im Neuenheimer Feld 293 (URZ)
eMail: jakob.schluttig@iwr.uni-heidelberg.de
WWW: http://www.bioms.de/schwarz

Most proteins in the cell are active in complexes with up to hundreds of different components. The reversible process of assembly of proteins into large clusters is very difficult to study in molecular detail due to computing time limitations. In our work we aim at combining the specifity of biomolecular simulation with the efficiency of stochastic modelling. As bridge between the two areas we use the concept of an 'encounter complex'. This concept has been successfully used before both in the context of molecular computer

simulation and stochastic models within the two participating groups. Here we describe first progress in modelling the diffusional part of the assembly process in the framework of Langevin equations and mean first passage time calculations.

Correlated ab initio QM/MM studies of enzymes

Walter Thiel

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim
eMail: thiel@mpi-muelheim.mpg.de
WWW: http://www.kofo.mpg.de/thiel

In recent years, it has become possible to model chemical reactions in large biomolecules using combined quantum mechanical / molecular mechanical (QM/MM) methods. After a general outline of the theoretical background and the chosen strategy [1], the lecture will focus on the use of high-level correlated ab initio methods in a QM/MM context, in particular coupled cluster theory, multi-reference configuration interaction, and multi-reference perturbation theory. The current possibilities and limitations of such approaches will be illustrated with several examples that include p-hydroxybenzoate hydroxylase and chorismate mutase [2] as well as cytochrome P450cam and related model systems [3,4].

[1] H. M. Senn and W. Thiel, Top. Curr. Chem. **268**, 173-290 (2007)
[2] F. Claeyssens, J. N. Harvey, F. R. Manby, R. Mata, A. J. Mulholland, K. E. Ranaghan, M. Schütz, S. Thiel, W. Thiel, and H.-J. Werner, Angew. Chem. Int. Ed. **45**, 6856-6859 (2006)
[3] J. C. Schöneboom, F. Neese, and W. Thiel, J. Am. Chem. Soc. **127**, 5840-5853 (2005)
[4] A. Altun, B. Engels, R. Fink, D. Kumar, F. Neese, and W. Thiel, to be published

New *ab initio* multi-configuration approaches designed for QM/MM applications

Reinhold F. Fink and Bernd Engels

Institute of Organic Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany
eMail: fink@chemie.uni-wuerzburg.de
WWW: http://www-organik.chemie.uni-wuerzburg.de/ak_engel

A vast variety of scientifically, technically and biologically interesting properties is related to open-shell electronic structure. Its proper description makes it necessary to use several electronic configurations (multi configuration) already as a starting point of the electronic wavefunction. This is the case for Cytochrome P450, a super family of enzymes which is involved in 80% of the degradation processes in the liver. The multi-configuration character of the target of the present project – the regio- and stereospecific hydroxylation of camphor by $P450_{cam}$ – is briefly indicated.

The treatment such extended multi-configuration systems is still hampered by (i) a lack of adequate methods and (ii) the substantial computational effort connected with existing approaches. For these reasons

(i) Retaining the Excitation degree Perturbation Theory (RE-PT) [1] was developed. It is a general method which fulfills all properties of a well defined theory in *ab initio* Quantum Chemistry. I.e. it is strictly size-consistent, unitary-invariant and systematically-improvable, like Møller-Plesset (MP) perturbation theory and Coupled Cluster (CC) methods. On the example of small model systems we demonstrate the capabilities of RE-PT for multi-configuration cases. It is shown that RE-PT is one of the few methods that allow to improve multi-configuration electronic wavefunctions systematically.

(ii) Concepts for improving the computational efficiency of multi-configuration approaches were investigated. In particular, the enormous reduction of the configurational space by the pair natural orbital (PNO) technique and the newly developed difference-density variant of the self-consistent-electron-pair (SCEP) method are discussed. We demonstrate that this makes calculations feasible in which multi-reference methods are used for the hydroxylation reaction of camphor by $P450_{cam}$ in quantum-mechanical/molecular-mechanical (QM/MM) calculations.

[1] R. F. Fink, Chem. Phys. Lett. **428**, 461 (2006)

Photoisomerisation in liquid azobenzene studied by nonadiabatic QM/MM simulations

Nikos L. Doltsinis, Marcus Böckmann, and Dominik Marx

Lehrstuhl für Theoretische Chemie, Ruhr-Universität Bochum, D-44780
eMail: `nikos.doltsinis@theochem.rub.de`
WWW: `www.theochem.rub.de/~nikos.doltsinis`

A nonadiabatic extension of ab initio molecular dynamics (AIMD) has been developed recently making possible the study of photoactivated processes in comparatively large — in particular condensed phase — systems containing up to a few hundred atoms (e.g. [1-4]). This approach is based on density functional theory and couples the Kohn-Sham electronic ground state to the restricted open-shell Kohn-Sham (ROKS) first excited singlet

state using Tully's surface hopping method.

In the present work, we have connected this nonadiabatic AIMD method to classical (force field) MD using the `CPMD` / `GROMOS` interface developed by Laio et al. [5]. This enables us to describe light-induced phenomena on a much increased length scale, treating only the chromophore quantum-mechanically and the complex environment classically. Our new nonadiabatic QM/MM approach has been applied to study photoisomerisation in liquid azobenzene as a first step towards modelling optically active materials. In the MM part we have used an especially adapted force field which we have optimized for the simulation of azobenzene compounds [6].

[1] N. L. Doltsinis and D. Marx, Phys. Rev. Lett. **88**, 166402 (2002)
[2] N. L. Doltsinis and D. Marx, J. Theor. Comp. Chem. **1**, 319 (2002)
[3] H. Langer and N. L. Doltsinis, Phys. Chem. Chem. Phys. **6**, 2742 (2004)
[4] H. Langer, N. L. Doltsinis, and D. Marx, ChemPhysChem **6**, 1734 (2005)
[5] A. Laio, J. VandeVondele, and U. Rothlisberger, J. Chem. Phys. **116**, 6941 (2002)
[6] M. Böckmann, C. Peter, L. Delle Site, N. L. Doltsinis, K. Kremer, and D. Marx, J. Chem. Phys. , (submitted)

Classical simulations from the atomistic to the mesoscale: coarse-graining an azobenzene containing liquid crystal

Christine Peter, Matej Praprotnik, Luigi Delle Site, Kurt Kremer

Max-Planck-Institute for Polymer Research, Ackermannweg 10, 55128 Mainz
eMail: `peter@mpip-mainz.mpg.de`
WWW: `http://www.mpip-mainz.mpg.de/~dellsite/multiscale`

Photoactive liquid crystalline systems are characterized by a wide range of relevant length and time scales - from the quantum mechanical to the mesoscopic level. Processes on different scales interplay and mutually influence each other, e.g. in azobenzene (AB) containing liquid crystals the photoisomerization of the AB unit induces a liquid crystalline phase transition, whereas on the other hand the anisotropic liquid crystalline environment potentially influences the photoisomerization mechanism. In order to capture these interplaying effects in molecular simulation, it is necessary to link quantum mechanical to classical simulations and force-field microscopic to coarse-grained mesoscopic descriptions.

We describe a multiscale modeling approach, where we – in collaboration with the group of D. Marx in Bochum – simulate the photoisomerization of the azobenzene unit in a liquid crystalline (LC) compound and the thus induced phase transition. In this contribution, we focus on the classical atomistic and the mesoscale simulations of the LC phase with special emphasis on methodological aspects of the coarse graining procedure.

Since the aim of the chosen multiscale simulation ansatz is to adaptively switch between resolutions when and where necessary, we also present recent developments performed in the Mainz group on an Adaptive Resolution Scheme (AdResS) for hybrid atomistic/mesoscale molecular dynamics simulations.

[1] M. Böckmann, C. Peter, L. Delle Site, N. L. Doltsinis, K. Kremer, D. Marx, submitted to J. Chem. Phys. , (2007)
[2] M. Praprotnik,L. Delle Site, K. Kremer, J. Chem. Phys. **123**, 224106 (2005)
[3] M. Praprotnik,L. Delle Site, K. Kremer, Phys. Rev. E **73**, 066701 (2006)

A new way of implementing partial slip boundary conditions

Jens Smiatek[1], Friederike Schmid[1], Ulf D. Schiller[2], Burkhard Dünweg[2], Michael P. Allen[3]

[1]Condensed matter theory, Universität Bielefeld, Fakultät für Physik, D-33615 Bielefeld, Germany
[2]Max Planck Institute for Polymer Research, Theory Group, D-55128 Mainz, Germany
[3]Department of Physics and Centre for Scientific Computing, University of Warwick, Coventry CV4 7Al, United Kingdom
eMail: smiatek@physik.uni-bielefeld.de, uschille@mpip-mainz.mpg.de
WWW: www.physik.uni-bielefeld.de/theory/cm
WWW: www.mpip-mainz.mpg.de/theory.html

Partial slip boundary conditions determine the flow profile in the micrometer scale of modern separation devices where evidence is found that the famous macroscopic no slip boundary conditions are no longer applicable.
In the first part of this joint talk we present a new approach to implement partial slip boundary conditions in Dissipative Particle Dynamics. A viscous layer is introduced in the vicinity of the boundaries. Crucial parameter for the boundary conditions are the slip length and the position of the hydrodynamic boundaries. The presented method allows to tune the slip length systematically and an approximate analytic equation for the slip length and the hydrodynamic boundary positions as a function of the model parameters can be derived. Comparison with simulations show that this expression is valid over a wide range of parameters.
In the second part of the talk we will outline, how the partial slip boundary condition can be adopted to the Lattice Boltzmann method. The key problem is to determine the unknown lattice populations at the boundary. We present a new approach to determine the equilibrium distribution of the Lattice Boltzmann model, which allows to incorporate the boundary conditions as additional constraints. This approach provides insights into

the effects of the reduced symmetry at the boundary and a strictly local implementation of boundary conditions seems possible.

NB: Partial slip boundary conditions, microscopic flow profiles, Dissipative Particle Dynamics, Lattice Boltzmann, slip length

Electrohydrodynamics in bulk and in confined geometries

Kai Grass[1], **Marcello Sega**[1], **Christian Holm**[1,2]

[1] Frankfurt Institute for Advanced Studies, Max-von-Laue-Strasse 1, D-60438 Frankfurt
[2] Max-Planck-Institute for Polymer Research, Ackermannweg 10, D-55128 Mainz
eMail: c.holm@fias.uni-frankfurt.de
WWW: http://www.fias.uni-frankfurt.de/~simbio

We investigate the electrohydrodynamic properties of short strongly charged polyelectrolytes in bulk by means of coarse-grained molecular dynamics simulations. By comparing a purely implicit treatment of the solvent with a Lattice Boltzmann modelled fluid, we show that hydrodynamic interactions are not screened on short length scales and have to be included to correctly model the experimentally observed behaviour [1,2]. Our results with the LB fluid show a maximum in the electrophoretic mobility of short oligomers, before saturating to the free draining limit for large polymers.

This effect becomes even more important, when the system is geometrically strongly confined such as in a narrow slit pore. The correct treatment of the dielectric boundary conditions for the confining media is ensured by a newly developed extension of the MMM2D and P3M+ELC algorithms for electrostatics [3].

With these tools at hand we report also on simulations aimed at studying the electroosmotic flow in a slit pore by means of coupled Molecular Dynamics - Lattice Boltzmann techniques. The influence of the dielectric jump is investigated and compared with theoretical predictions.

[1] Böhme, U. and Scheler, U., Colloids and Surfaces A **222**, 35–40 (2003)
[2] Cottet, H., Gareil, P., Theodoly, O. and Williams, C.E., Electrophoresis **21**, 3529–3540 (2000)
[3] Tyagi, S., Arnold, A., and Holm, C., ICMMM2D: An accurate method to include planar dielectric interfaces via image charge summation , submitted ()

Simulating electrostatic and Lifshitz interactions in inhomogeneous dielectric media

I. Pasichnyk[1], S. Pasquali[3] R. Everaers[1,2], A.C. Maggs[3]

[1]Max Planck Institute for the Physics of Complex Systems, Noethnitzer Str. 38, D-01187 Dresden, Germany.
[2]Laboratoire de Physique, ENS Lyon, 46, allée d'Italie, F-69007 Lyon, France.
eMail: pasichny@mpipks-dresden.mpg.de, ralf.everaers@ens-lyon.fr
[3]PCT CNRS-7083, ESPCI, 10 rue Vaquelin 75005, Paris.
eMail: samuela@turner.pct.espci.fr, tony@turner.pct.espci.fr
WWW: http://www.pct.espci.fr/~tony
WWW: http://www.mpipks-dresden.mpg.de/~everaers/index.html

Many macromolecules carry ionizable side-groups and contain hydrophobic as well as hydrophilic parts. Since the non-polar elements typically have a very low dielectric constant compared to water, electrostatic (solvation) self-energies and charge-charge interactions have to be evaluated in dielectrically inhomogeneous media. We present a new family of algorithms which generate long ranged electrostatic interactions *dynamically* via *local* interactions between charges, the medium and the electric field. In particular, the approach allows the description of non-linear and non-local dielectric media at practically unchanged computational costs.

In addition, the algorithm generates the non-retarded, classical (Keesom) part of the Lifshitz-interaction which dominates van der Waals-interactions in systems composed of water and hydrocarbons. We show that this interaction can be studied in more detail by mapping the partition function onto a determinant, which we evaluate with sparse matrix techniques. The method generalizes to the non-retarded quantum interaction. We illustrate the non-additivity of interactions between a sharp point and surface indentation.

Self-organized, noise-free escape of coupled nonlinear oscillator chains

D. Hennig[1], L. Schimansky-Geier[1], P. Hänggi[2]

[1] Institute of Physics, Humboldt-University at Berlin, Newton Str. 15, D-12489 Berlin
eMail: hennigd@physik.hu-berlin.de, alsg@physik.hu-berlin.de
[2] Institute of Physics, University Augsburg, Universitätsstr. 1, D-86135 Augsburg, Germany
eMail: hanggi@physik.uni-augsburg.de

We consider the self-organized escape of a chain of harmonically coupled units from a

metastable state over a cubic potential barrier. The underlying dynamics is conservative and purely deterministic. The supply of a sufficient total energy transforms the chain into the nonlinear regime from which an initially, nearly uniform lattice configuration becomes unstable, yielding a redistribution with a strong localization of energy. A spontaneously emerging localized mode grows into the critical nucleus. Upon passing this transition state, the nonlinear chain performs a collective, deterministic escape event. Surprisingly, we find that such noise-free, collective nonlinear barrier crossing events yield a drastically diminished average escape time as compared to the one that is assisted by continuously impacting thermal noise. This beneficial enhancement of the rate of escape for the chain typically occurs whenever the ratio between the average energy supplied per unit in the chain and the potential barrier energy assumes small values.

Transport in nanopores

I.D. Kosinska, I. Goychuk, G. Schmid, P. S. Burada, and P. Hänggi

Institut für Physik, Universität Augsburg, Universitätsstr. 1, D-86135 Augsburg
eMail: Ilona.Kosinska@physik.uni-augsburg.de
WWW: http://www.physik.uni-augsburg.de/theo1/hanggi/

Ion transport in biological and synthetic nanochannels is characterized by such phenomena as ion current fluctuations, and rectification. Recently, it has been shown that the nanofabricated synthetic pores can mimic some transport properties of biological ion channels [1,2].

The ion current rectification is studied within the reduced 1D PNP model for synthetic pores. A conical channel of nm to a few hundred of nm in diameter, and of μm long is considered in the limit where the channel length exceed much the Debye screening length. The channel wall is assumed to be weakly charged. Ion transport is described by the nonequillibrium steady-state solution of the Poisson-Nernst-Planck system within a singular perturbation treatment. The role of boundary conditions is discussed.

[1] P. Yu. Apel et al, Nucl. Instrum. Methods Phys. Res. B **184**, 337 (2001)
[2] Z. Siwy et al., Europhys. Lett. **60**, 349 (2002)

Interphase microtubule organization of fission yeast.

Rose Loughlin, Marcel Janson, Phong Tran, Damian Brunner and Francois Nedelec

European Molecular Biology Laboratory Heidelberg, 69117 Heidelberg
eMail: nedelec@embl.de
WWW: http://www.cytosim.org/

The fission yeast Schizosaccharomyces pombe maintains a cylindrical shape by alternating polarized growth at the cell ends with divisions in the middle. The localized growth is established during interphase by four to six bundles of microtubules that deposit growth factors specifically at cell ends. The bundles are organized with the plus- ends of microtubules pointing outwards, and minus-ends forming an anti-parallel overlap near the cell center. I will present some recent observations made on this system, and a computational model in which the bundles are organized by the action of molecular motors and crosslinkers. I will compare the model with bundles in wild-type cells, and in mutant cells lacking some of the essential components.

[1] Janson et al., Cell **128**, 357–368 (2007)

Proteamalg: a new tool for prediction of the substrate degradation and fragment production by the proteasome

A. Zaikin[1] and M. Mishto[2]

[1]Department of Mathematics, University of Essex, Wivenhoe Park, Colchester, CO4 3SQ, UK
[2] Department of Experimental Pathology, University of Bologna, 40126, Bologna, Italy
eMail: zaikin@essex.ac.uk
WWW: http://www.essex.ac.uk/maths/staff/zaikin/index.shtm

Proteasomes are multicatalytic enzyme complexes responsible for degradation of the majority of the proteins and production of epitopes for MHC class I antigenic pathway. I will discuss several mathematical models that simulate the proteasome function. Mainly I will focus on the description of the new algorithm Proteamalg [1] that enables the prediction of the substrate degradation and fragment production. This algorithm uses the solution of kinetic differential equations to describe the dynamics of the fragment concentration. The algorithm successfully describes the dynamics of concentrations, the deceleration of short peptide degradation, and an effect of the regulation particle PA28 on the production of

double and single cleavage products. Finally, I will discuss that it would be important to include in quantitative modelling the results recently obtained by us in the investigation of the proteasome transport properties [2-5].

[1] M. Mishto, A. Zaikin et al., (to be submitted) , (2007)
[2] A. Zaikin, A.K. Mitra, D. Goldobin, and J. Kurths, Biophysical Reviews and Letters **1**, 375 (2006)
[3] A. Zaikin and J. Kurths, Journal of Biological Physics **32**, 231 (2006)
[4] F. Luciani and A. Zaikin, in "Irreversible Prozesse und Selbstorganisation", Logos-Verlag, Berlin , 195 (2006)
[5] A. Zaikin and T. Poeschel, Europhysics Letters **69**, 725 (2005)

Cytoplasm and integrin dynamics in a 2D continuum model for cell migration

Esa Kuusela and Wolfgang Alt

University of Bonn / Department of Theoretical Biologie, Kirschallee 1, 53115 Bonn
eMail: `kuusela@uni-bonn.de`
WWW: `http://www.theobio.uni-bonn.de`

Certain types of cells, e.g. keratinocytes, have the ability to move on surfaces with appropriate adhesive coating. The essential cell functions for motion are at least the continuous polymerization, depolymerization and deformation of intra-cellular actin filament network, as well as the evolution of cell membrane bound integrin protein structures that can mediate the network generated forces to the underlying surface.

We will here describe a large scale continuum model capable of treating these microscopic processes. The 2 dimensional model consists of two layers. The top layer describes the interior of the cell as a two-phase fluid where the components are the highly viscous dynamic filament network and the low viscous intra-cellular liquid, the cytosol [1]. The bottom layer consist of the integrin molecules in the basal membrane. The integrin molecules can bound both to the outside substrate and to the actin filament network inside the cell and thus form adhesion cites capable of delivering the actin network flow to a protusive force [2].

The model is able to show many of the characteristics of moving keratinocytes like rapid protrusion and retrograde flow of actin network. We consider the actin network flow in several geometries describing the leading tip of moving cell and whole cell fragment. The formation of adhesion sites is shown. We will also study progressively moving cell fragments and their integrin dynamics.

[1] W. Alt and M. Dembo, Math. Biosci. **156**, 207 (1999)

[2] C. Möhl, Diploma Thesis , page 33 (2005)

The physics of an ear

Björn Nadrowski

Institute of Zoology, University of Cologne, Weyertal 119, 50923 Köln
eMail: bjoern.nadrowski@uni-koeln.de
WWW: http://www.pks.mpg.de/~bn

Ears are prime examples of complex dynamical systems. Their workings rely on a multitude of macroscopic, cellular, and molecular components, they are essentially nonlinear and operate away from thermal equilibrium. Inside the ear, sound-induced vibration of nanometer dimensions are funneled to specialized, mechanosensitive ion channels that transduce them into electrical responses. This auditory transcduction is an active process: It expends energy to nonlinearly amplify the sound-induced vibrations, thus increasing the ear's sensitivity to faint sound. Identifying the physical principles that govern this elementary process of auditory transduction is essential for our understanding of how hearing works. In *Drosophila*, hearing is mediated by the antenna. Stimulus forces acting on the antennal receiver are coupled to dedicated sensory cells that comprise the molecular machinery for mechanosensory transduction, adaptation and amplification.

We present a comprehensive theoretical description based on the gating spring model of mechanotransduction in vertebrate hair cells. This description captures the response of the fly's ear to small stimuli, its response to force steps, its fluctuations, its linear response function, activity and nonlinear amplification, and the time course of the electrical response in the antennal nerve. Our findings allow to mechanistically and quantitatively link transduction, adaptation, and amplification in an intact auditory system and show that the molecular module defined by the gating spring model of mechanotransduction is sufficient to describe the performance of an entire ear. Furthermore, these findings suggest that while the auditory anatomies of flies and vertebrates are vastly different, the molecular components and mechanisms that promote fly and vertebrate hearing are strikingly similiar.

Profiting from the experimental and genetic tractability provided by *Drosophila*, and combining experimental, theoretical, and numerical approaches, this approach is a starting point for exploring the dynamic properties and integrated workings of an auditory system, spanning from molecular dynamics to systemic performance.

4 Abstracts – Poster

Brownian dynamics simulations on a lattice

Denitsa Alamanova, Ines Hörger, Volkhard Helms

Center for Bioinformatics, University of Saarland, 66123 Saarbruecken
eMail: volkhard.helms@bioinformatik.uni-saarland.de
WWW: http://gepard.bioinformatik.uni-saarland.de

Protein protein association involves processes on different length and time scales. At large distances, only the relative motion of the two centers of mass is important. In this regime, the free energy landscape can be sampled either by brownian dynamics or Monte Carlo simulations, or by a grid search. At close distances, the internal degrees of freedom and the molecular nature of the solvent become of crucial importance. So far, no efficient approaches exist that allow computing the interaction in this regime except for the final, bound state. Miyashita and co-workers [1] have determined the positions of encounter and transition states at those regions where the computed energy differences between wildtype and mutant proteins fit to experimental data on binding kinetics and strength. This approach allows, at least, to approximate the energy surface at close distances.

In order to provide an efficient method to simulate macromolecular diffusion as well as association and dissociation events, we are aiming at a dual description. Here, the spatial dynamics of individual proteins takes place on a coarse grained lattice, while the association dynamics, which is governed by the local interactions, is mapped onto a protein association network, where association is described by adding a link and dissociation by link removal. The required association and dissociation rates may be fitted against experimental or computational data.

Here we present results for the spatial component of this hybrid approach, i.e., the problem of how to correctly model diffusion on a coarse grid, given the microscopic diffusion coefficient. In contrast to the time independent random walk methods, our requirement is that transition probabilities are modeled correctly for jumps beyond the next neighbors, too. From the condition that such a propagation should reproduce the diffusive evolution of a free particle at finite times, we derive a condition for discretizing the stepsizes for arbitrary gridspacings, timesteps and diffusion coefficients.

[1] Miyashita, O., Onuchic, J. N., and Okamura, M. Y. , PNAS **101**, 16174 (2004)

CONCOORD/PBSA: A Versatile Method for the Prediction of Mutant Free Energy & Structure

Alexander Benedix[1], Bert de Groot[2], Amedeo Caflisch[3], and Rainer A. Böckmann[1]

[1]Theoretical & Computational Membrane Biology, Center for Bioinformatics Saar, Saarland University, D-66041 Saarbrücken, Germany
[2]Computational Biomolecular Dynamics Group, MPI for Biophysical Chemistry, Göttingen
[3]Department of Biochemistry, University of Zürich, Switzerland
eMail: `rainer@bioinformatik.uni-saarland.de`
WWW: `www.bioinf.uni-sb.de/RB`

The reliable and fast computation of the free energy of proteins is crucial for structure-based protein design or for protein docking algorithms. Rigorous treatments involve computationally expensive methods like free energy perturbation approaches, which are, however, incompatible with the need for fast methods. Commonly used fast methods, in turn, involve empirically derived scoring functions and usually do not include the protein flexibility. Hence, such methods are inherently limited in accuracy. We propose a physical effective energy function for a fast and quantitative estimation of the free energy of mutants, a measure for their conformational stability. The first step involves the fast generation of alternative protein conformations based on geometric considerations only (CONCOORD [1]), aimed at efficiently sampling the available configurational space. Subsequently, an energy function which is based on physical chemistry (force field) and an efficient continuum solvent approach (solution of the Poisson-Boltzmann equation, nonpolar solvation) is averaged over the generated ensemble. The entropic contribution is estimated by an harmonic approximation of the sampled degrees of freedom, thereby taking the respective specific environment and changes therein into account. Together, these two steps — the generation of alternative conformations and the computation of effective free energies — allow an accurate and efficient estimation of relative free energies, without applying molecular dynamics simulations. The correlation achieved for a test set of 579 mutants was 0.72 with a standard deviation of 1.0 kcal/mol. The main advantage of this method with respect to empirically derived scoring functions is the inclusion of full flexibility and the fast sampling of conformational space.

[1] B. de Groot *et al.*, Proteins **29**, 240 – 251 (1997)

Probing the Photoswitch: non-adiabatic Hybrid QM/MM MD Studies of Liquid Azobenzene

Marcus Böckmann, Nikos Doltsinis, Dominik Marx

Lehrstuhl für Theoretische Chemie, Ruhr-Universiät Bochum, Universitätsstr. 150, 44801 Bochum, Germany
eMail: marcus.boeckmann@theochem.rub.de
WWW: www.theochem.rub.de

Polymeric materials containing the azobenzene moiety are of increasing interest because of their photoswitchable macroscopic properties due to the light-induced *E–Z* isomerisation of the central nitrogen double bond [1,2]. Realistic models of such systems are typically too large to be treated by means of pure ab initio molecular dynamics (AIMD). Classical atomistic force fields, on the other hand, are not parametrized to deal with photoexcitations. The challenge to theory is to embed microscopic quantum mechanical methods to investigate the photoinduced reaction in the excited electronic state into atomistic force field methods for studying large scale systems including polymers. We have combined the ROKS-DFT based Surface Hopping method [3] for non-adiabatic excited state AIMD with the hybrid quantum–classical QM/MM approach [4] implemented in the CPMD Package [5].

Currently we study the photoisomerisation of a single azobenzene chromophore in bulk liquid azobenzene at 400 K. In close cooperation with our colleagues at the Max-Planck Institute for Polymer Research (Mainz) we have established an atomistic force field description adapted for QM/MM simulations for the fundamental azobenzene building block [6].

Taking different starting conditions obtained from equilibrated ground state trajectories, we perform non-adiabatic excited state AIMD runs on the liquid azobenzene system (comprising 343 AB molecules) as well as on a single azobenzene molecule in the gas phase. Comparing the results for the liquid system to the gas phase data, implications of the environment to the photoswitching process of the azobenzene chromophore will be discussed.

An envisaged future extension of this overall approach will include coarse-grained methods to fully link the atomistic description to the macroscopic description [7].

[1] Z. Sekkat and W. Knoll, eds., Photoreactive organic thin films , Academic Press (2002)
[2] J. Wachtveitl, S. Spörlein, H. Satzger, B. Fonrobert, C. Renner, R. Behrendt, D. Oesterhelt, L. Moroder, and W. Zinth, Biophys. J. **86**, 2350 (2004)
[3] N.L. Doltsinis and D. Marx, Phys. Rev. Lett. **88**, 166402 (2002)
[4] A. Laio, J. VandeVondele, and U. Röthlisberger, J. Chem. Phys. **116**, 6941-6947 (2002)
[5] CPMD, Copyright IBM Corp 1990-2006, Copyright MPI für Festkörperforschung Stuttgart 1997-2001 , (2006)

[6] M. Böckmann, C. Peter, L. Delle Site, N.L. Doltsinis, K. Kremer, and D. Marx, J. Chem. Phys , submitted (2007)
[7] M. Praprotnik, L. Delle Site, and K. Kremer, J. Chem. Phys. **123**, 224106-224120 (2005)

Chromatin Organization on Large and Small Scales

Manfred Bohn and Dieter W. Heermann

Institute for Theoretical Physics, University of Heidelberg, 69120 Heidelberg
eMail: bohn@tphys.uni-heidelberg.de

Recent experiments conducted in Roel van Driel's lab in Amsterdam [1] yielded differences in the compaction between highly transcribed regions (RIDGEs) and regions with low transcriptional activity (AntiRIDGEs). We compare *FISH* measurements of the spatial vs. genomic distance on human interphase chromosomes to the prediction of three basic polymer models relevant for modelling the chromatin fiber, namely random walk, self-avoiding walk and globular state models. The random walk model assumes the bond angles to be completely uncorrelated and ignores excluded volume interactions. The self-avoiding walk model takes excluded volume into account. Additionally the globular state model takes temperature-dependent attractive intra-chain interactions into account acting as a counterpart on excluded volume interactions. For all these models the mean square displacement scales like $\langle \mathbf{R}^2 \rangle = l^2 \, N_m^{2\nu}$ (in the limit of large contour length N_m), differing only in the exponent ν. We show that only the globular state can reconcile both recent data and data by Yokota et. al. published in the 90ies [2] on small scales (below 3 Mb). On larger length scales, the globular state still shows the correct leading order behaviour, deviations might be explained by loop-building.

[1] Julio Mateos-Langerak, Osdilly Giromus, Wim de Leeuw, Jens Odenheimer, Manfred Bohn, Gregor Kreth, Dieter W. Heermann, Roel van Driel, and Sandra Goetze, *(preprint)* , (2007)
[2] H. Yokota, G. van den Engh, J. Hearst, R. Sachs. & B. Trask, J. Cell Biol. **130**, 1239-1249 (1995)

Advanced Molecular Dynamics and Umbrella Sampling of DNA bending and backbone dynamics

Jeremy Curuksu, Krystyna Zakrzewska, Martin Zacharias

International University Bremen, School of Engineering and Science, Campus Ring 6, D-28759 Bremen
eMail: j.curuksu@iu-bremen.de

The bending flexibility of DNA plays a major role in many biological functions such as spatial organization of the chromatin in eukaryotic cells (wrapping around nucleosomes), protein-DNA binding and gene regulation. Unfortunately, standard molecular dynamics (MD) simulations do not allow sampling of kinked or strongly bend DNA conformations as observed in packed DNA or many protein-DNA complexes. To systematically investigate the structural details of DNA bending and to characterize bending pathways in structural and energetic terms we carried out energy minimization and Umbrella Sampling MD simulation studies. A new bending angle restraining variable was developed that is a geometric construction involving every rotational degree of freedom of N inter-nucleotide junctions at both ends of a DNA fragment. The approach was tested on several DNA sequences indicating that this approach can monitor global bending by distributing DNA conformational parameters optimally according to the specific dependence on the sequence (manuscript in prep.). The approach was applied systematically to several 15 base pair DNA oligonucleotides with different central sequences including A-tracts and alternating TA and CG sequences allowing us to extract also associated bending free energies. Simulations were also performed in the regime of high curvature on a 15-mer alternating CG sequence resulting in a single kink (un-stacking) at a peripheral CpG step. Such local kinks have recently been suggested to explain formation of small DNA circles smaller than the persistence length of DNA [1,2,3]. This structural transition is, however, irreversible during the simulation. A proper sampling of the CpG kinking pathway requires more innovative sampling techniques such as the Hamiltonian Replica Exchange method [4] by using the bending biasing potential as a replica coordinate. This technique may avoid strongly bent conformations to get trapped in a local minimum state associated with a single kink through exchanges of conformations with the low bending window replicas. Results on a systematic comparison with standard Umbrella Sampling will be presented.

[1] Cloutier TE, Widom J , Mol Cell. **14**, 355 (2004)
[2] Wiggins PA, et al., Phys. Rev. E. Stat. Nonlin. Soft Matter Phys. **71**, 021909 (2005)
[3] Lankas F, Lavery R, Maddocks JH., Structure **14**, 1527 (2006)
[4] Fukunushi H, Watanabe O, Takada S, J. Chem. Phys. **116**, 9058 (2002)

QM/MM characterization of irreversible inhibitors

R. F. Fink[1], M. Mladenovic[1], W. Thiel[2], and B. Engels[1]

[1]Institute of Organic Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany
[2]Max-Planck-Institute for coal research, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim, Germany
eMail: fink@chemie.uni-wuerzburg.de
WWW: http://www-organik.chemie.uni-wuerzburg.de/ak_engel

Cysteine proteases are widely distributed in living organisms, from bacteria to humans. Being involved in many diseases they represent promising drug targets for osteoporosis, arthritis, cancer, Alzheimers disease and for a vide variety of parasitic infections such as malaria or African trypanosomiasis ("sleeping sickness").

A typical irreversible cysteine protease inhibitor consists of an electrophilic building block, e.g. an epoxide or aziridine ring attached to a peptidic or peptidomimetic sequence [1]. In the inhibition mechanism these highly active three membered rings cleave building a chemical bond that blocks the active site of the enzyme permanently.

We present theoretical studies of enzyme inhibitor interactions using quantum mechanical/molecular mechanical (QM/MM) approach. This is required as the covalent bond cleavage and formation can only be treated accurately using quantum mechanics (QM). The protein environment properly mimics the enzyme surrounding.

Different theoretical methods and surroundings were applied to describe the irreversible step of the cysteine protease inhibition reaction. A QM/MM method is established in which the explicit protein environment is described using molecular modelling (MM) and the inhibitor and the Cys29 and His199 of the active site of the enzyme are treated quantum mechanically.

Combination of the theoretical and experimental studies provide particularly detailed insight into the inhibition mechanism such that even a rational design of these inhibitor class becomes feasible [2,3].

[1] R. Vicik, M. Busemann, C. Gelhaus, N. Stiefl, J. Schreiber, W. Schmitz, F. Schulz, M. Mladenovic, B. Engels, M. Leippe, K. Baumann, and T. Schirmeister, Chem Med Chem **1**, 1126 (2006)
[2] R. Vicik, H. Helten, T. Schirmeister, and B. Engels, Chem Med Chem **1**, 1021 (2006)
[3] M. Mladenovic, T. Schirmeister, S. Thiel, W. Thiel, and B. Engels, ChemMedChem **2**, 120 (2007)

Probing the size-dependent diffusion of membrane inclusions and nonequilibrium fluctuations of lipid bilayers with mesoscopic simulations

Gernot Guigas, Matthias Weiss

Cellular Biophysics Group (BIOMS), B085, German Cancer Research Center, Im Neuenheimer Feld 580, 69120 Heidelberg, Germany
eMail: m.weiss@dkfz.de
WWW: http://www.dkfz.de/en/cellular_biophysics/index.html

Experimentally determined diffusion constants are often used to elucidate the size and oligomeric state of membrane inclusions, e.g. rafts. This approach critically relies on the knowledge of the size-dependence of diffusion. We have used mesoscopic simulations to elucidate the size-dependent diffusion of membrane inclusions. For small radii R we find that the lateral diffusion coefficient D is well described by the Saffman-Delbruck relation, yet for large radii we observe an asymptotic scaling $D \sim 1/R^2$ which originates from the asymptotic hydrodynamics and the inclusion's internal degrees of freedom. In contrast, the rotational diffusion constant D_r follows the predicted hydrodynamic scaling $D_r \sim 1/R^2$ over the entire range of considered radii.

We also have studied the effect of active membrane inclusions on the non-equilibrium mechanics of lipid bilayers. The inclusions correspond to two-state integral membrane proteins that change between an open and a closed state, leading to a renormalization of the bending rigidity (as calculated from the fluctuation spectrum) and the area compression modulus. The results show that the observed softening of the membrane is logarithmically dependent on the activity of the inclusions and varies with their concentration. Also, the diffusion of the active inclusions is strongly enhanced with their activity.

[1] Guigas & Weiss, Biophys. J. **91**, 2393 (2006)
[2] Weiss, Jakobsen & Mouritsen, submitted , ()

Conductance properties of DNA molecular wires

R. Gutierrez, D. Ryndyk, B. Song, and G. Cuniberti

Insitute for Theoretical Physics, University of Regensburg, D-93040 Regensburg, Germany
eMail: rafael.gutierrez@physik.uni-r.de
WWW: http://www-mcg.uni-r.de/

A fundamental precondition for DNA to act as a molecular wire is its capability to support an electric current. The partially contradictory electrical transport experiments in

the last years have presented a challenge to theoreticians.Many factors have turned out to be essential in determining charge propagation in DNA: the quality of the molecule-metal contacts, the specific base-pair sequence, environmental effects, and structural fluctuations, among others. In our research, we have mainly addressed the influence of the environment and internal vibrational excitations on the quantum transport characteristics of short DNA molecular wires. Structural fluctuations can be e.g. a source of dissipation and decoherence for propagating charges and thus dramatically affect the transport properties of the molecule. In view of the complexity of the target system, we have adopted a Hamiltonian-model approach, which allows to identify and filter out individual factors controlling charge transport in DNA. Our results have demonstrated e.g. the emergence, inside the molecular HOMO-LUMO gap, of environment-induced virtual states which may strongly modify the low-energy transport in DNA wires. Presently, we are working along two main lines to further develop our approach: (i) Hamiltonian parametrization via density-functional calculations and molecular dynamics simulations of realistic DNA configurations, and (ii) implementation of charge-vibron interactions in the non-equilibrium regime via Keldysh Green function techniques.These research lines will allow a closer and more realistic contact to DNA electrical transport experiments.

Microcanonical analysis of polymer aggregation

Christoph Junghans[1,2], Michael Bachmann[1,3], and Wolfhard Janke[1]

[1]Institut für Theoretische Physik, Universität Leipzig, Augustusplatz 10/11, D-04109 Leipzig
[2]Max Planck Institute for Polymer Research, P.O. Box 3148, D-55021 Mainz
[3]Computational Biology & Biological Physics Group, Department of Theoretical Physics, Lund University, Sölvegatan 14A, SE-223 62 Lund
eMail: `bachmann@thep.lu.se`
WWW: `www.physik.uni-leipzig.de/~bachmann/smsrg.html`

We propose the use of microcanonical analyses for numerical studies of peptide aggregation transitions [1]. Performing multicanonical Monte Carlo simulations of a simple hydrophobic-polar continuum model for interacting heteropolymers of finite length, we find that the microcanonical entropy behaves convex in the transition region, leading to a negative microcanonical specific heat. As this effect is also seen in studies of phase separation transitions of other finite systems, our results provide clear evidence for recent hints that the characterisation of phase separation in first-order-like transitions of small systems profits from this microcanonical view [2].

[1] C. Junghans, M. Bachmann, and W. Janke, Phys. Rev. Lett. **97**, 218103 (2006)
[2] D. H. E. Gross and J. F. Kenney, J. Chem. Phys. **122**, 224111 (2005)

Exploring the Conformational Space of Biomolecules by Biasing Potential Replica Exchange Molecular Dynamics Simulations

Srinivasaraghavan Kannan, Martin Zacharias

International University Bremen, School of Engineering and Science, Campus Ring 6, D-28759 Bremen
eMail: skannan@iu-bremen.de

The application of classical molecular dynamics (MD) simulations for studying biomolecules is limited by the accuracy of current force fields and the simulation time scale. Peptides and proteins can adopt several locally stable conformations separated by high energy barriers. Conformational transitions between these stable states can therefore be rare events even on the time scale of tens to hundreds of nanoseconds simulation time. Among the various methods proposed to tackle the sampling problem, replica exchange molecular dynamics (RexMD) simulation is a successful method to enhance the conformational sampling [1]. However, it is limited to small systems since the number of required replicas increases with increasing system size. In the current work an alternative Hamiltonian replica-exchange method is proposed that focuses on the biomolecule backbone flexibility and employs a biasing potential to promote backbone transitions as a replica coordinate. The aim of this bia sing potential is to reduce the energy barriers associated with peptide backbone dihedral transitions. The level of biasing is gradually changed along the replicas such that frequent transitions are possible at high levels of biasing and thus the system can escape from getting trapped in local energy minima. Since exchanges between replicas are independent of the number of solvent molecules our method requires much fewer replicas for efficient sampling compared to standard temperature RexMD. This Biasing Potential Replica Exchange MD (BP-RexMD) [2] has been systematically applied to study the conformational sampling of various peptides (alanine and threonine dipeptides, a hexa alanine peptide and a beta hairpin forming peptide) and a small protein. The BP-RexMD method showed in all cases significantly better sampling of conformational space compared to the standard MD simulations with a small number of required replicas (5-7). The method is also well suited to improve the sampling of conformational sub-states in nucleic acids and extensions to study nucleic acids will be presented.

[1] Sugita Y, Okamoto Y, Chem. Phys. Lett **314**, 141 (1999)
[2] Kannan S, Zacharias M, Proteins **66**, 697 (2007)

Simulation of transport through OmpF channels

U. Kleinekathöfer, S. Pezeshki. C. Chimerel, M. Winterhalter

School of Engineering and Science, Jacobs University Bremen[1], Campus Ring 1, 28759 Bremen
eMail: u.kleinekathoefer@iu-bremen.de
WWW: http://www.faculty.iu-bremen.de/ukleinekat/

The outer membrane protein F (OmpF) trimer is a pore in the outer membrane of *Escherichia coli*. Since the crystal structure of OmpF is known, molecular dynamics simulations are possible [1,2]. Applying a constant electric field, the current caused by potassium and chlorine ions can be determined directly. Good agreement with experimental data is achieved [3]. In the constriction zone, i.e. the narrowest part of the pore, we additionally mutated charged amino acids to neutral ones. With the help of these mutated OmpF structures we investigated the influence of charged and neutral constriction zones on the ionic current. In a second step we are simulating the translocation of antibiotics molecules through the pore.

[1] K. M. Robertson and D. P. Tieleman, FEBS Lett. **528**, 53 (2002)
[2] W. Im and B. Roux, J. Mol. Biol. **319**, 1177 (2002)
[3] E. M. Nestorovich, C. Danelon, M. Winterhalter, and S. M. Bezrukov, PNAS **99**, 9789 (2002)

Probability for specific bond formation for a Brownian particle in linear shear flow above a wall

Christian B. Korn[1,2] and Ulrich S. Schwarz[2]

[1] Max Planck Institute of Colloids and Interfaces, D-14424, Potsdam, Germany
[2] University of Heidelberg, Im Neuenheimer Feld 293, D-69120 Heidelberg, Germany
eMail: Christian.Korn@iwr.uni-heidelberg.de
eMail: Ulrich.Schwarz@iwr.uni-heidelberg.de

Cohesion in biological systems and biotechnological applications is usually provided by specific bonds between receptors and ligands. The formation of these bonds requires a physical transport process which brings receptors and ligands to sufficient proximity for binding.
As a non-trivial example here we study the motion of a rigid spherical Brownian particle in linear shear flow carrying receptors for ligands covering a planar boundary wall. This

[1] formerly International University Bremen

situation is relevant for the binding of white blood cells to blood vessel walls, which can be studied quantitatively in flow chambers. The appropriate mobility matrix follows from the Stokes equation and is position-dependent due to the presence of the wall. This leads to a non-trivial multiplicative noise term in the corresponding Langevin equation.
We determine the mean time for receptor-ligand encounter as a function of the Péclet numbers, which describe the transition from diffusive to deterministic transport. We also show in quantitative detail how the results are influenced by the number and the geometry of receptor and ligand patches.

[1] C. Korn and U. S. Schwarz, Phys. Rev. Lett. **97**, 138103 (2006)
[2] C. B. Korn and U. S. Schwarz, J. Chem. Phys. **126**, 095103 (2007)

Dynamic simulation of active and inactive chromatin domains

G. Kreth, J. Odenheimer, D.W. Heermann

Heidelberg University, Kirchhoff Institute for Physics/INF 227, Institute of Theoretical Physics/Philosophenweg 19, 69120 Heidelberg
eMail: gkreth@kip.uni-heidelberg.de

Presently, a rosette like structure of chromatin loops is assumed to exist for the experimentally observed chromosomal foci. On the basis of the 30nm fiber a polymer model was implemented which allows the dynamic folding in rosette like structures when attractive sites were distributed along the fiber. The spatial versus genomic distance patterns for different numbers of attrative sites were compared with experimental distance measurements on chromosome one in gene ridge and anti ridge parts of the chromosome. A crucial question is the accessibility of these rosettes for proteines, e.g. transcription factor complexes. Presently there still two opinions about the aggregation process of transcription and splicing factors. They might form functional complexes directly at the sites of genes. Alternatively, (sub-) complexes are built up at distant sites, in the so called interchromatin regions, and subsequently reach the genes by passive diffusion. In the later case, such aggregates are in the order between 55 and 70nm in diameter and have to access the active genes to allow transcription. Brownian Dynamics simulations of rosettes/proteine complexes were performed to investigate the dynamics and the accessibility of the both components. These simulations revealed a not accessible region inside of the 3D rosette structure.

Molecular Dynamics Simulations using Temperature Enhanced Essential dynamics Replica EXchange (TEE-REX).

Marcus B. Kubitzki and Bert L. de Groot

Computational biomolecular dynamics group
Max Planck Institute for Biophysical Chemistry
Am Fassberg 11
37077 Goettingen, Germany
eMail: bgroot@gwdg.de
WWW: http://www.mpibpc.mpg.de/groups/de_groot

Todays standard molecular dynamics (MD) simulations of moderately sized biomolecular systems at full atomic resolution are typically limited to the nanosecond timescale and therefore suffer from limited conformational sam- pling. Efficient ensemble-preserving algorithms like replica exchange (REX) may alleviate this problem somewhat but are still computationally pro- hibitive due to the large number of degrees of freedom involved. Aiming at increased sampling efficiency we present a novel simulation method com- bining the ideas of essential dynamics and replica exchange. Unlike stan- dard REX, in each replica only a selection of essential collective modes of a subsystem of interest (essential subspace) are coupled to a higher temper- ature with the remainder of the system staying at a reference temperature T0 . This selective excitation along with the replica framework permits efficcient approximate ensemble-preserving conformational sampling and allows much larger temperature differences between replicas, thereby considerably enhancing sampling efficiency. Ensemble properties and sampling perfor- mance of the method are discussed using dialanine and guanylin test sys- tems with multi-microsecond MD simulations of these test systems serving as reference.

[1] M. B. Kubitzki and Bert L. de Groot, Biophys. J. , in press. (2007)

Collective Langevin Dynamics of Conformational Motion in Proteins

Oliver F. Lange[1] and Helmut Grubmüller[2]

[1] Biochemistry Department, University of Washington, Seattle, USA
[2] Max-Planck-Institute für biophysikalische Chemie, Göttingen
eMail: olange@u.washington.edu
WWW: http://www.mpibpc.gwdg.de/groups/grubmueller

Functionally relevant slow conformational motions of proteins are, at present, in most cases inaccessible to molecular dynamics MD simulations. The main reason is that the major part of the computational effort is spend for the accurate description of a huge number of high frequency motions of the protein and the surrounding solvent. The accumulated influcence of these fluctuations is crucial for a correct treatment of the conformational dynamics; however, their details can be considered irrelevant for most purposes. To accurately describe long time protein dynamics we proposed a reduced dimension approach, collective Langevin dynamics CLD , which evolves the dynamics of the system within a small subspace of relevant collective degrees of freedom. The dynamics within the low-dimensional conformational subspace is evolved via a generalized Langevin equation which accounts for memory effects via memory kernels also extracted from short explicit MD simulations. To extract suitable collective degrees of freedom from molecular dynamics trajectories a full quantization of correlation is crucial, which was achieved using signal processing techniques.

Coarse–grained simulation approaches to chromatin dynamics

Jörg Langowski

German Cancer Research Center, Division Biophysics of Macromolecules, Im Neuenheimer Feld 580, D-69120 Heidelberg, Germany
eMail: `jl@dkfz.de`
WWW: `http://www.dkfz.de/Macromol`

We present a number of coarse-grained approaches to simulating the structure and dynamics of chromatin, ranging from single nucleosomes to the 30 nm chromatin fiber. Based on the known crystallographic structure of the nucleosome and on all-atom molecular dynamics, effective force fields are developed which allow dynamic simulations of mononucleosomes over 0.5 μs in a one-bead-per-residue approximation.

For larger length and time scales, the DNA is approximated by a segmented polymer chain and the nucleosomes by rigid cylinders which interact through different salt-dependent interaction potentials. This approach, originally proposed by Wedemann and Langowski [1] allows for the prediction of possible higher-order structures and their mechanical properties. As examples, we show the unrolling of DNA from the histone core, the response of the 30 nm chromatin fiber to mechanical stretching [2] and possible regimes of stable and unstable packing of chromatin.

[1] G. Wedemann, J. Langowski, Biophys. J. **82**, 2847-59 (2002)
[2] F. Aumann, F. Lankas, M. Caudron, J. Langowski, Phys. Rev. E **73(4)**, 041927 (2006)

Designed Flexible Fusogenic Transmembrane Domains in TFE

David Minde

Biopolymer Chemistry, Weihenstephaner Berg 3, 85354 Freising
eMail: DavidMinde@gmail.com
WWW: http://www.wzw.tum.de/biopolymere

Fusion of biological membranes is a highly dynamic process taking place on a sub-millisecond time-scale [1], [2]. Integral membrane proteins e. g. soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins regulate this fast process that plays a crucial role in biology. Their membrane-extrinsic domains apparently mediate early steps of fusion. Later steps seem to require TransMembrane Domains (TMDs) because their replacement or mutation can hinder completion of the fusion process [3], [4]. The structural and functional analysis of biological fusogenic TMDs has suggested a correlation of structural plasticity and fusogenicity [5]. The recent *de novo* design of conformationally flexible fusogenic domains supports this model. In addition, it contributed a set of various synthetic peptides which vary significantly in conformational stability in 2,2,2-TriFluoroEthanol (TFE) and fusogenicity at the same time [6]. Most of the structural dynamics has been measured with Circular Dichroism (CD) spectroscopy. Functional data have been obtained n vitro with TMDs reconstituted into lipid vesicles. The corresponding time-scales range within minutes to hours and represent averages of very large ensembles. In addition, the fusion rates in such a vesicle assay are a combination of the rates of membrane apposition and later fusion steps. Membrane apposition is relatively slow in the absence of membrane-extrinsic SNARE domains. Single-molecule studies indicate millisecond rates of later fusion steps [7].

Molecular Dynamics (MD) simulation studies, however, can readily handle the picosecond time-scales for single proteins or peptides in various solvents. A recent MD study modelled the energetics of fusion of two whole, protein-free vesicles on a sub-millisecond time-scale [8]. Currently, there is still much to be learnt about the intricate interaction of fusogenic peptides with their changing complex environment. Resulting effects on structural peptide dynamics on very short times scales are apparently significant for biological fusion.

This study analyzes two designed peptides of significantly different fusogenicity. A correlation between fusogenicity and intrinsic peptide flexibility has been found at all levels of analysis in a 80 % TFE box simulation on a very short time scale from picoseconds to several nanoseconds. For example, secondary structure as well as Connolly surfaces fluctuated significantly more in the fusogenic LV16-P8G9 peptide than in the much less fusogenic L16 peptide. In addition, strong H-bonds were significantly less frequent in the LV16-P8G9 trajectory. Moreover, the global geometry analysis of the peptides revealed marked differences on this very short time scale. An extension of this study might shed more light on ultra-fast peptide dynamics underpinning biological fusion in its native context.

[1] B. L. Sabatini and W. G. Regehr, Nature **384**, 170–172 (1996)
[2] B. L. Sabatini and W. G. Regehr, Annu Rev Physiol **61**, 521–542 (1999)
[3] E. Grote, M. Baba, Y. Ohsumi and P. J. Novick, J Cell Biol **151**, 453–466 (2000)
[4] J. Rohde, L. Dietrich, D. Langosch, C. Ungermann, J Biol Chem **278**, 1656–1662 (2003)
[5] D. Langosch, J. M. Crane, B. Brosig, A. Hellwig, L. K. Tamm and J. Reed, J Mol Biol **311**, 709–721 (2001)
[6] M. W. Hofmann, K. Weise, J. Ollesch, P. Agrawal, H. Stalz, W. Stelzer, F. Hulsbergen, H. de Groot, K. Gerwert, J. Reed and Dieter Langosch, PNAS **101**, 14776-14781 (2004)
[7] T. Liu, W. C. Tucker, A. Bhalla, E. R. Chapman and J. C. Weisshaar, Biophys J **89**, 2458–2472 (2005)
[8] P. M. Kasson, N. W. Kelley, N. Singhal, M. Vrljic, A. T. Brunger and V. S. Pande, PNAS **103**, 11916-11921 (2006)

A simple network model shows significance of the topology in protein folding dynamics

Majid Mosayebi, M. Reza Ejtehadi

Department of Physics, Sharif University of Technology, Tehran, 14588-89694, Iran
eMail: `mosayebi@physics.sharif.edu`
WWW: `http://physics.sharif.edu/softmatter`

Protein folding is one of the most basic self assembly processes in the cell that is very difficult to explain in details. Some recent experimental and theoretical studies show that in the complicated folding process there are some simple governing rules which could control the dynamics and mechanism of the process [1]. For example there are a significant correlation between folding rate of two-state proteins and their relative contact order [2,3].

In this work we apply a Gō-like [4] dynamics on a network to study how topology affects the folding process. The network's nodes represent the protein's monomers and any link between the network nodes is considered as a contact between the protein monomers. The contact reduce the structural energy if and only if they overlap with native(target) contacts. This simple and dimensional free model perfectly simulate two-state folding dynamics of proteins.

The model is improved by adding chemical links between the monomers and considering the distance between the nodes in a 3-dimensional space. This makes our network more similar to the real protein chains and let us to assign contact order to their native network. Monte Carlo simulations on this 3D network model of protein folding show correlation between logarithm of folding rate and relative contact order of the chain. However the correlation is strong enough if we simply take a random network as native contacts network, it is more significant if the network of the native state has a small world [5] topology as it is supported with other studies [6,7]. In the later case we found the value of 0.84 for

correlation coefficient between the rate and contact order which is interestingly close to the reported value of real proteins [2,3].

[1] D. Baker, Nature **405**, 39 (2000)
[2] K. W. Plaxco, K. T. Simons and D. Baker, J. Mol. Biol. **277**, 985 (1998)
[3] K. W. Plaxco, K. T. Simons, I. Ruczinski and D. Baker, Biochemistry **39**, 11177 (2000)
[4] N. Go, Ann. Rev. Biophys. Bioeng. **12**, 183 (1983)
[5] D. J. Watts and S. H. Strogatz, Nature **393**, 440 (1998)
[6] A. Rana Atilgan, P. Akan and C. Baysal, Biophys. J. **86**, 85 (2004)
[7] M. Vendruscolo, N. V. Dokholyan, E. Paci and M. Karplus, Phys. Rev. E **65**, 061910 (2002)

Dynamic Protonation State Analysis of Dsb Proteins

Daniele Narzi and Rainer A. Böckmann

Theoretical & Computational Membrane Biology, Center for Bioinformatics Saar, Saarland University, D-66041 Saarbrücken, Germany
eMail: {narzi,rainer}@bioinformatik.uni-saarland.de
WWW: www.bioinf.uni-sb.de/RB

Disulfide bond formation and rearrangement is of the central importance for the correct folding and stability of several proteins. In prokaryotes this process is catalyzed by Dsb proteins. The highly oxidizing DsbA protein introduces disulfide bonds in the substrate by reduction of its cysteine pair placed in the active site. Subsequently it is reoxidized by the inner membrane protein DsbB, which transports electrons to the ubiquinone. Rearrangement of wrong disulfide bonds is achieved by the DsbC/D proteins which catalyze the reduction of disulfide bonds of misfolded proteins [1].

Here we investigated by molecular dynamics (MD) simulations and protonation state analysis the functional properties of various Dsb proteins. The pKa analysis involved the background interaction energy, the pair wise interaction energy between the titratable groups, as well as the desolvation energy. The inclusion of hydration entropy was found to be important for the correct description of the protonation states of the active site cysteines. We show that tiny structural changes may induce proton transfer from the active site cysteine pair to specific buried residues which we suggest to act as a proton source or sink crucial for the function of the Dsb proteins.

[1] C. U. Stirnimann, A. Rozhkova, U. Grauschopf, R. A. Böckmann, R. Glockshuber, G. Capitani, M. G. Grütter, J.Mol.Biol. **358**, 829 – 845 (2006)

Simulation of linker histone in chromatin fiber

Georgi V. Pachov, Rebecca C. Wade

Molecular and Cellular Modeling Group, EML Research gGmbH, Schloss-Wolfsbrunnenweg 33, 69118 Heidelberg
eMail: georgi.pachov@eml-r.villa-bosch.de
WWW: http://www.eml-research.de/mcm

The dynamics and interaction between protein-protein and protein-DNA molecules appearing on different time and length scales in the cell are of fundamental interest. In chromatin, linker histone binds to the highly charged nucleosome particle driven by electrostatic attraction. However, its position and orientation with respect to the nucleosome core as well as its binding sites are unresolved problems. Using implicit representation of the surrounding molecules, rigid-body docking of linker histone to the nucleosome particle (SDA software) has been performed revealing how the protein binds to DNA on the nucleosome. Simulation of diffusional motion of both molecules for computation of the association rates and encounter complex formation is under study with SDA. The results will be integrated in higher-order simulation of chromatin fiber.

Simulating van der Waals-interactions in water/hydrocarbon-based complex fluids

I. Pasichnyk[1], R. Everaers[1,2], A.C. Maggs[3]

[1]Max Planck Institute for the Physics of Complex Systems, Noethnitzer Str. 38, D-01187 Dresden, Germany
eMail: pasichny@pks.mpg.de
[2]Laboratoire de Physique, ENS Lyon, 46, allée d'Italie, F-69007 Lyon, France
eMail: ralf.everaers@ens-lyon.fr
[3]Laboratoire de Physico-Chimie Théorique, UMR CNRS–ESPCI 7083, 10 rue Vauquelin, F-75231 Paris Cedex 05, France
eMail: tony@turner.pct.espci.fr

Van der Waals-interactions in systems composed of water and hydrocarbons are dominated by the non-retarded, classical (Keesom) part of the Lifshitz-interaction, can be screened by salt ions and extend over mesoscopic distances of the order of the size of the (micellar) constituents of complex fluids. We show that these interactions are generated implicitly by a recently introduced local Monte Carlo algorithm for simulating electrostatic interactions between charges in the presence of non-homogeneous dielectric media.

Lateral diffusion of proteins in fluctuating membranes

Ellen Reister-Gottfried, Stefan M. Leitenberger, and Udo Seifert

II. Institut für Theoretische Physik, Universität Stuttgart, Pfaffenwaldring 57, 70550 Stuttgart, Germany
eMail: reister@theo2.physik.uni-stuttgart.de

Measurements of lateral diffusion of proteins in a membrane typically assume that the movement of the protein occurs in a flat plane. Real membranes, however, are subject to thermal fluctuations, leading to movement of an inclusion into the third dimension. Therefore, the equation of motion governing the dynamics of a diffusing protein becomes a function of the membrane shape. Estimates for the difference between the actual intra-membrane diffusion coefficient and the diffusion coefficient that follows from the projection of the protein path on a flat plane will be presented. These results were obtained both through analytical calculations that use a preaveraging approximation that assumes membrane fluctuations to be much faster than protein diffusion, and stochastic simulations that do not rely on this kind of approximation.

It is very likely that a laterally diffusing protein interacts with the shape of the membrane. This interaction will of course influence the diffusive behaviour. In our work this interaction is introduced as a coupling of the diffusing particle to the local membrane curvature. Results for the altered protein diffusion will be presented that were achieved through approximate analytical calculations and extensions of the above mentioned simulation scheme.

Simulating electroosmotic flow using Lattice Boltzmann technique

Marcello Sega[1], Christian Holm[1,2]

[1] Frankfurt Institute for Advanced Studies, Max-von-Laue-Strasse 1, D-60438 Frankfurt
[2] Max-Planck-Institute for Polymer Research, Ackermannweg 10, D-55128 Mainz
eMail: c.holm@fias.uni-frankfurt.de
WWW: http://www.fias.uni-frankfurt.de/~simbio

We present recent results on simulation of electroosmotic flow in a slit pore by means of coupled Molecular Dynamics - Lattice Boltzmann techniques. The use of recently developed extensions for the ELC algorithm for electrostatics allows us to treat the proper dielectric boundary conditions for the confining media. The influence of the dielectric jump on the confining plates is investigated and compared with theoretical predictions.

Towards a universal free energy forcefield for all atom protein folding

Abhinav Verma, Srinivasa M. Gopal and Wolfgang Wenzel

INT, Forschungszentrum Karlsruhe, Postfach 3640, 76021, Karlsruhe
eMail: verma@int.fzk.de
WWW: www.fzk.de/biostruct

Protein folding and prediction of its tertiary structure is one of the central problems of computational biophysics. Various forcefields have been developed to model the protein structure. As the protein structures are very diverse, the transferability of the forcefield is the key requirement. The protein forcefield (PFF01 [1]), earlier developed in our group, was successfully used to model helical proteins. Now, it has been generalized to include proteins of other types. The generalized version (PFF02 [2]) correctly predicts the native structure of various proteins at its global minimum, starting from completely extended conformations. Using PFF02, along with stochastic optimization methods [3], we were able to fold a wider range of proteins including helical proteins (Tryptophan cage 1L2Y, HIV accessory protein 1F4I, Staphylococcal Protein A B/E domain 1BDD/1EDK, Engrailed Homeodomain protein 1ENH, potassium channel blocker 1WQE, E6 binding tryptophan cage 1RIJ, BBA motif 1T8J), several beta hairpins (Tryptophan zippers 1LE0/1LE1, HIV V3 loops 1NIZ, 1U6U, three stranded GSGS peptide, HP7 2EVQ) and mixed (helix + sheet) systems (E6 binding zinc finger 1RIK). PFF02 emerges as a transferable free energy forcefield that locates the native state of a protein at the global minimum at its free energy surface.

[1] T. Herges and W. Wenzel, Biophys. J. **87**, 3100 (2004)
[2] A. Verma and W. Wenzel, submitted , (2007)
[3] A. Verma, A. Schug, K. H. Lee and W. Wenzel, J. Chem. Phys. **124**, 044515 (2006)

5 Participants

Prof. Dr. Ahlrichs, Reinhart reinhart.ahlrichs@chemie.uni-karlsruhe.de
Institut für Physikalische Chemie, 76128 Karlsruhe, Germany

Dr. Alamanova, Denitsa deni_aleman@yahoo.com
Center for Bioinformatics, Saarland University, 66041 Saarbrücken, Germany

Prof. Dr. Alt, Wolfgang wolf.alt@uni-bonn.de
Theoretical Biology, Univ. Bonn, 53115 Bonn, Germany

Dr. Bachmann, Michael bachmann@thep.lu.se
Department of Theoretical Physics, Lund University, SE-223 62 Lund, Sweden

Dr. Bischler, Ulrike bischler@volkswagenstiftung.de
VolkswagenStiftung, 30519 Hannover, Germany

Dr. Böckmann, Marcus Marcus.Boeckmann@theochem.rub.de
Lehrstuhl für Theoretische Chemie, Ruhr-Universität Bochum, 44801 Bochum, Germany

Dr. Böckmann, Rainer rainer@bioinformatik.uni-saarland.de
Center for Bioinformatics Saar, Saarland University, 66041 Saarbrücken, Germany

Bohn, Manfred bohn@tphys.uni-heidelberg.de
Institut für Theoretische Physik, 69120 Heidelberg, Germany

Caudron-Herger, Maiwen caudron@kip.uni-heidelberg.de
Kirchhoff-Institut fur Physik, 69120 Heidelberg, Germany

Dr. Delle Site, Luigi dellsite@mpip-mainz.mpg.de
Max-Planck Institute for Polymer Research, 55128 Mainz, Germany

Dr. Doltsinis, Nikos nikos.doltsinis@rub.de
Lehrstuhl fuer Theoretische Chemie, 44801 Bochum, Germany

Dr. Dünweg, Burkhard duenweg@mpip-mainz.mpg.de
Max Planck Institute for Polymer Research, 55128 Mainz, Germany

Prof. Dr. Engels, Bernd bernd@chemie.uni-wuerzburg.de
Institut für Organische Chemie, 97074 Würzburg, Germany

Dr. Everaers, Ralf ralf.everaers@ens-lyon.fr
Laboratioire de Physique, ENS Lyon, 69364 Lyon cedex 07, France

Prof. Dr. Fink, Reinhold fink@chemie.uni-wuerzburg.de
Institute of Physical Chemistry, 97074 Würzburg, Germany

Dr. Fischer, Stefan stefan.fischer@iwr.uni-heidelberg.de
IWR / Computational Biochemistry Group, 69120 Heidelberg, Germany

Dr. Gabdoulline, Razif R. gabdoulline@eml.org
EML Research gGmbH, 69118 Heidelberg, Germany

Prof. Dr. Gompper, Gerhard G.Gompper@fz-juelich.de
Forschungszentrum Jülich GmbH, 52425 Jülich, Germany

Grass, Kai grass@fias.uni-frankfurt.de
Frankfurt Institut for Advanced Studies, 60438 Frankfurt, Germany

Dr. de Groot, Bert bgroot@gwdg.de
Max Planck Institute for Biophysical Chemistry, 37077 Goettingen, Germany

Prof. Dr. Grubmüller, Helmut hgrubmu@gwdg.de
Max-Planck-Institut für biophysikalische Chemie, 37077 Göttingen, Germany

Guigas, Gernot g.guigas@dkfz.de
DKFZ Heidelberg, 69120 Heidelberg, Germany

Prof. Dr. van Gunsteren, Wilfred wfvgn@igc.phys.chem.ethz.ch
ETH Zrich, CH-8093 Zrich, Switzerland

Dr. Gutierrez, Rafael rafael.gutierrez@physik.uni-r.de
University of Regensburg, 93040 Regensburg, Germany

Prof. Dr. Hänggi, Peter hanggi@physik.uni-augsburg.de
Institut für Physik, 86159 Augsburg, Germany

Prof. Dr. Heermann, Dieter W. heermann@tphys.uni-heidelberg.de
Institut für Theoretische Physik, 69120 Heidelberg, Germany

Hellmann, Marcel hellmann@tphys.uni-heidelberg.de
Institut für Theoretische Physik und DKFZ, 69120 Heidelberg, Germany

Prof. Dr. Helms, Volkhard volkhard.helms@bioinformatik.uni-saarland.de
Center for Bioinformatics, Saarland University, 66041 Saarbrücken, Germany

Dr. Hennig, Dirk hennigd@physik.hu-berlin.de
Institut für Physik, 12489 Berlin, Germany

Dr. Holm, Christian c.holm@fias.uni-frankfurt.de
Frankfurt Institut for Advanced Studies, 60438 Frankfurt, Germany

Prof. Dr. Jäger, Willi wjaeger@iwr.uni-heidelberg.de
IWR, 69120 Heidelberg, Germany

Dr. Jeremy, Curuksu j.curuksu@iu-bremen.de
International University Bremen, 28759 Bremen, Germany

Dr. Kannan, Srinivasaraghavan s.kannan@iu-bremen.de
International University Bremen, 28759 Bremen, Germany

Dr. Kepper, Nick nick@kip.uni-heidelberg.de
KIP, University of Heidelberg, 69120 Heidelberg, Germany

Prof. Dr. Kleinekathöfer, Ulrich u.kleinekathoefer@iu-bremen.de
School of Engineering and Science, Jacobs University Bremen, 28759 Bremen, Germany

Korn, Christian christian.korn@iwr.uni-heidelberg.de
IWR - BIOMS, 69120 Heidelberg, Germany

Dr. Kosinska, Ilona D. Ilona.Kosinska@physik.uni-augsburg.de
Institut für Physik, 86159 Augsburg, Germany

Prof. Dr. Kremer, Kurt kremer@mpip-mainz.mpg.de
Max Planck Institute for Polymer Research, 55128 Mainz, Germany

Kreth, Gregor gkreth@kip.uni-heidelberg.de
Kirchhoff Institute for Physics, 69120 Heidelberg, Germany

Dr. Kuusela, Esa kuusela@uni-bonn.de
Theoretical Biology, Univ. Bonn, 53115 Bonn, Germany

Dr. Lange, Oliver olange@u.washington.edu
University of Washington, Seattle WA 98195, USA

Prof. Dr. Langosch, Dieter langosch@lrz.tum.de
TU München, 85354 Freising, Germany

Prof. Dr. Langowski, Jörg jl@dkfz.de
Deutsches Krebsforschungszentrum, 69120 Heidelberg, Germany

Dr. Maggs, Anthony tony@turner.pct.espci.fr
ESPCI-CNRS, Paris, 75231 Cedex, France

Prof. Dr. Mark, Alan a.e.mark@uq.edu.au
University of Queensland, 4072 St Lucia, Australia

Prof. Dr. Marx, Dominik office@theochem.rub.de
Lehrstuhl für Theoretische Chemie, Bochum, 44801 Bochum, Germany

Minde, David D.Minde@lrz.tum.de
TU München, 85354 Freising, Germany

Dr. Moritsugu, Kei Kei.Moritsugu@iwr.uni-heidelberg.de
IWR, University of Heidelberg, 69120 Heidelberg, Germany

Mosayebi, Majid mosayebi@physics.sharif.edu
Department of Physics, Sharif University of Technology, Tehran, Iran

Müller-Klieser, Stefan stefan.mueller-klieser@web.de
Universität Heidelberg, 69117 Heidelberg, Germany

Dr. Nadrowski, Björn bjoern.nadrowski@uni-koeln.de
Zoologisches Institut, Universität Köln, 50923 Köln, Germany

Narzi, Daniele narzi@bioinformatik.uni-saarland.de
Center for Bioinformatics Saar, Saarland University, 66041 Saarbrücken, Germany

Dr. Nedelec, Francois nedelec@embl.de
EMBL, 69117 Heidelberg, Germany

Dr. Pachov, Georgi V. georgi.pachov@eml-r.villa-bosch.de
EML Research gGmbH, 69118 Heidelberg, Germany

Dr. Pasichnyk, Igor pasichny@pks.mpg.de
Max-Planck-Institute for the Physics of complex Systems, 01187 Dresden, Germany

Dr. Pasquali, Samuela samuela@turner.pct.espci.fr
PCT - ESPCI, Paris, 75231 Cedex, France

Dr. Peter, Christine peter@mpip-mainz.mpg.de
Max Planck Institute for Polymer Research, 55128 Mainz, Germany

Dr. Reister-Gottfried, Ellen reister@theo2.physik.uni-stuttgart.de
II. Institut fuer Theoretische Physik, Universitaet Stuttgart, 70550 Stuttgart, Germany

Dr. Rippe, Karsten Karsten.Rippe@kip.uni-heidelberg.de
Kirchhoff-Institut für Physik, 69120 Heidelberg, Germany

Schiller, Ulf uschille@mpip-mainz.mpg.de
MPI for Polymer Research, 55128 Mainz, Germany

Prof. Dr. Schimansky-Geier, Lutz alsg@physik.hu-berlin.de
Institut für Physik, 12489 Berlin, Germany

Schluttig, Jakob jakob.schluttig@iwr.uni-heidelberg.de
IWR - BIOMS, 69120 Heidelberg, Germany

Schmidt, Ulrich ulrich.schmidt@dkfz-heidelberg.de
DKFZ Heidelberg, 69120 Heidelberg, Germany

Dr. Schwarz, Ulrich Ulrich.Schwarz@iwr.uni-heidelberg.de
BIOMS, 69120 Heidelberg, Germany

Dr. Sega, Marcello sega@fias.uni-frankfurt.de
Frankfurt Institut for Advanced Studies, 60438 Frankfurt, Germany

Smiatek, Jens smiatek@physik.uni-bielefeld.de
Universität Bielefeld, Fakultät fuer Physik, 33615 Bielefeld, Germany

Prof. Dr. Smith, Jeremy biocomputing@iwr.uni-heidelberg.de
Computational Molecular Biophysics Group, IWR, 69120 Heidelberg, Germany

Stehr, Rene rene.stehr@fh-stralsund.de
Fachhochschule Stralsund, 18435 Stralsund, Germany

Prof. Dr. Thiel, Walter thiel@mpi-muelheim.mpg.de
Max-Planck-Institut für Kohlenforschung, 45470 Mülheim, Germany

Prof. Dr. Tibken, Bernd tibken@uni-wuppertal.de
Uni Wuppertal, FB E, Lehrstuhl für Automatisierungstechnik/Regelungstechnik, 42119 Wuppertal, Germany

Dr. Verma, Abhinav verma@int.fzk.de
Forschungszentrum Karlsruhe, 76021 Karlsruhe, Germany

Warthenpfuhl, Sascha warthenpfuhl@uni-wuppertal.de
Uni Wuppertal, FB E, Lehrstuhl für Automatisierungstechnik/Regelungstechnik, 42119 Wuppertal, Germany

Prof. Dr. Wedemann, Gero gero.wedemann@fh-stralsund.de
FH Stralsund, 18435 Stralsund, Germany

Dr. Weiss, Matthias m.weiss@dkfz.de
DKFZ Heidelberg, 69120 Heidelberg, Germany

Dr. Willms-Hoff, Indra willms-hoff@volkswagenstiftung.de
VolkswagenStiftung, 30519 Hannover, Germany

Prof. Dr. Zacharias, Martin m.zacharias@iu-bremen.de
International University Bremen, 28759 Bremen, Germany

Dr. Zaikin, Alexey zaikin@essex.ac.uk
University of Essex, CO4 3SQ/Colcester, UK