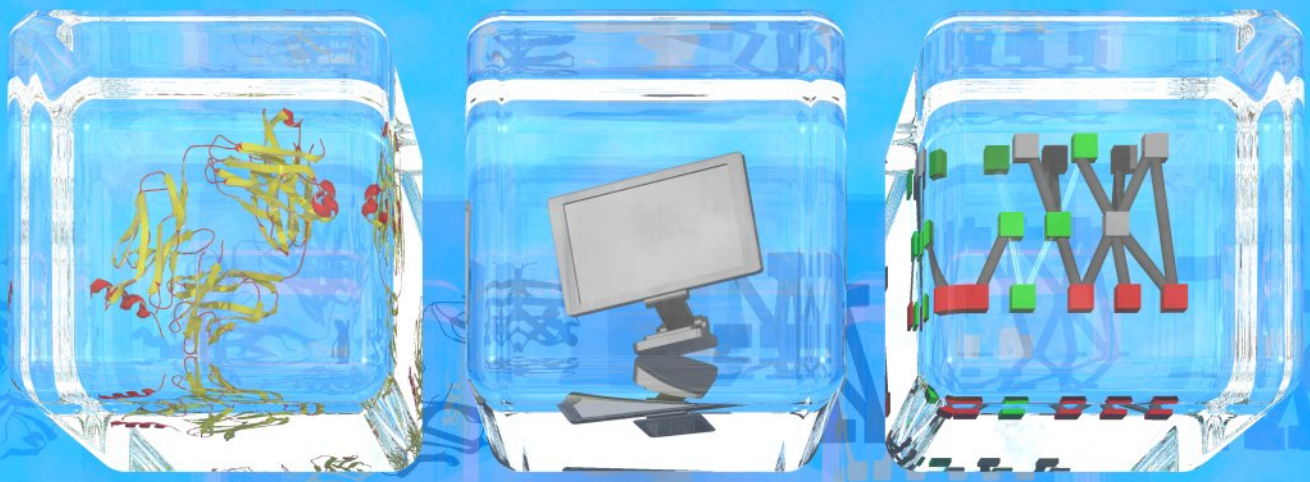
www.chemie.uni-erlangen.de/ccc/conference

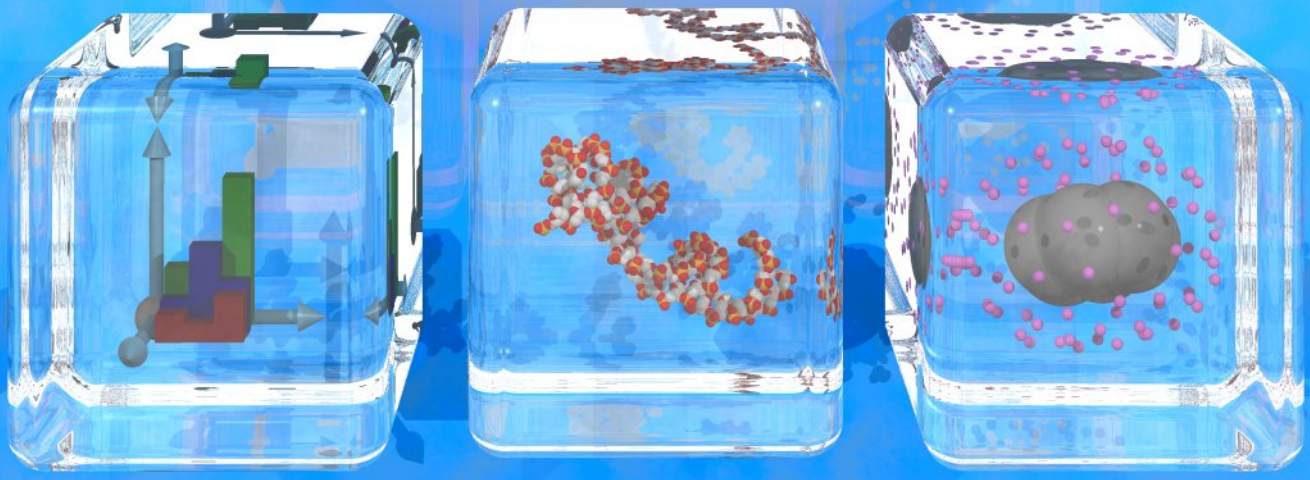


Molecular Modelling

25th

Workshop 2011

April, 4th - 6th



Friedrich-Alexander-Universität Erlangen-Nürnberg

Computer Chemie Centrum

MGMS molecular graphics modelling society

MOLECULAR MODELLING WORKSHOP 2011

Monday, April 4th - Wednesday, April 6th 2011

Computer-Chemie-Centrum
Nägelsbachstr. 25
91052 Erlangen, Germany

Once again, we in CCC are happy to welcome you to our annual Molecular Modelling Workshop 2011. This year, it is the 25th Workshop and the ninth time it is hosted by the University of Erlangen-Nuremberg. The research group of Prof. Tim Clark at the Computer-Chemie-Centrum, joined by those of Prof. Bernd Meyer and Prof. Dirk Zahn is responsible for the technical organization. Dr. Christian Kramer, Novartis, Basel, is responsible for the scientific organization.

The Molecular Graphics and Modelling Society – German Section e.V. (MGMS-DS e.V.) is, as always the organizer of the Workshop and provides financial support to enable students to attend the workshop. We especially thank our sponsors, who have not only this year enabled us to provide an excellent program at a very low price, but also have supported the Molecular Modelling Workshop consistently and generously over its entire history.

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DEAR COLLEGUES,

the 25th Molecular Modelling Workshop (April, 4th - 6th) provides research students and new postdoctoral scientists the perfect opportunity to present their research to the molecular modelling community. Scientists at the beginning of their academic careers are able to meet new colleagues in academia and industry.

Every year, we are happy to welcome both poster or lecture contributions in English or German from all areas of molecular modelling including life sciences, physical sciences, materials science and the nano sciences.

The aim of the Modelling Workshop is to introduce research in progress. The workshop is the perfect venue to present new methods in molecular modelling that can be applied to many disciplines. The workshop is suitable for everyone, those who want to gain experience in presentation skills and those who just want to network in a friendly relaxed environment.

This workshop encourages young scientists - especially graduate students - to present and discuss their research topics. Young scientists at the beginning of their academic careers will be able to meet new colleagues from academia and gain feedback from industrial colleagues.

Contributions are welcome
from all areas of molecular modelling -
from the life sciences, computational biology,
computational chemistry to materials sciences.

Our plenary speakers this year are:

JÜRGEN BRICKMANN

Molcad GmbH
Darmstadt

KENNETH M. MERZ, JR.

University of Florida
Gainesville

MARKUS MEUWLY

University of Basel

EMAD TAJKHORSHID

Beckman Institute
University of Illinois
Urbana-Champaign

AWARDS

As in the past years, there will be two Poster Awards of 100 Euro each and three Lecture Awards for the best talks:

Winner

Travel bursary to the Young Modellers Forum in the United Kingdom (travel expenses are reimbursed up to 500 Euro)

2nd Winner

200 Euro travel expenses reimbursement

3rd Winner

100 Euro travel expenses reimbursement

Only undergraduate and graduate research students qualify for the poster and lecture awards. A Web Award for WWW-based scientific applications in the field of molecular modelling will not be awarded this year.

MGMS-DS E.V. ANNUAL MEETING

The general meeting of the MGMS (German Section) will be held during the workshop. Please feel free to join us!

CONFERENCE FEE

The conference fee amounts to 50 Euro (Students: 25 Euro). This amount includes the annual membership fee for the MGMS-DS e.V. (15 Euro).

25 YEARS - 25 WORKSHOPS

We are very happy to announce that the tradition of the former Darmstadt Molecular Modelling workshop, now known as Molecular Modelling Workshop is carried into its 25th year. Since the first Darmstadt Molecular Modelling workshop was initiated by Prof. Jürgen Brickmann in June 1987, it was constantly held in Darmstadt every year until the conference loacation was moved to Erlangen in 2003. We are very happy to have not only Prof. Jürgen Brickmann as plenary lecturer, but also many participants who constantly supported the Molecular Moldelling Workshop throughout the last 24 years as guests in Erlangen this year.

Scientific coordinators of the 25 Workshops:

1st	**June 1987** Dr. E. Weber BMBF & Prof. J. Brickmann TH Darmstadt	**15th**	**May 2001** Dr. Gerd Moeckel Lion Bioscience Heidelberg
2nd	**May 1988** Dr. Barnickel Merck, Darmstadt	**16th**	**May 2002** Dr. Harald Lanig Univ. Erlangen
3rd	**May 1989** TH Darmstadt	**17th**	**May 2003** Dr. Beck & Dr. Teckentrup Boehringer Ingelheim Biberach
4th	**May 1990** TH Darmstadt	**18th**	**May 2004** Dr. Bernd Kallies Konrad-Zuse-Zentrum Berlin
5th	**May 1991** TH Darmstadt	**19th**	**May 2005** Dr. Harald Mauser Roche, Basel
6th	**May 1992** Dr. Willi von der Lieth TH Darmstadt	**20th**	**May 2006** Prof. Dr. Holger Gohlke Univ. Frankfurt am Main
7th	**May 1993** Dr. Stefan Kast TH Darmstadt	**21st**	**May 2007** Dr. Stefan Güssregen Sanofi-Aventis Frankfurt am Main
8th	**May 1994** TH Darmstadt	**22nd**	**April 2008** PD Dr. Wolfgang Brandt Leibniz Institute of Plant Biochemistry, Halle
9th	**May 1995** Dr. Michael Krug Merck, Darmstadt	**23rd**	**September 2009** Dr. Thomas Mietzner BASF AG, Ludwigshafen
10th	**May 1996** Prof. Dr. A. Geiger Univ. Dortmund	**24th**	**March 2010** Prof. Rainer Böckmann Univ. Erlangen
11th	**May 1997** Prof. Dr. H.-J. Lindner TH Darmstadt	**25th**	**April 2011** Dr. Christian Kramer Novartis, Basel
12th	**May 1998** Dr. Jens Sadowski BASF AG		
13th	**May 1999** Dr. Michael Krug Merck, Darmstadt		
14th	**May 2000** Dr. Andreas Dominik Byk Gulden, Konstanz		

PROGRAM

Monday, April 4th 2011

11:30-14:00	***Registration***
14:00-14:15	***Welcome remarks / Agenda review***
14:15-14:35	**Matthias Dietzen (Saarbrücken)** On the Applicability of Normal Modes in Small-Molecule Docking
14:35-14:55	**Simon Leis (München)** Efficient Inclusion of Receptor Flexibility in grid-based Docking
14:55-15:15	**Alexander Gayday (Kiev)** Computational And Experimental Studies Of New Cage Compounds - Potential Antiviral Drugs
15:15-16:15	**Plenary Lecture: Markus Meuwly (Basel)** Multipolar Force Fields in Chemical and Biological Simulations
16:15-16:35	***Coffee break***
16:35-16:55	**Richard Bradshaw (London)** Reliably and repeatably predicting free energies by combining MM-PBSA with LES
16:55-17:15	**Anna Katharina Dehof (Saarbrücken)** A Pipeline for the training of NMR chemical shift prediction models
17:15-17:35	**Zoran Miličević (Zagreb)** Water ordering around small hydrophobic solutes in electric fields
17:45-18:45	***Annual Meeting of the MGMS-DS e.V.***
19:00	***Poster Session and Buffet***

PROGRAM

Tuesday, April 5th 2011

08:30-08:50 **Jing Huang (Basel)**
Efficient Computational Methods for Transition Metal Complexes: Computational Characterization of a Hydrogen-Bonded Bidentate Catalyst

08:50-09:10 **Pavlo Dral (Erlangen)**
Modeling Molecular Electronic Properties with Semiempirical UNO-CAS

09:10-09:30 **Martin Richter (Jena)**
SHARC - ab initio molecular dynamics with surface hopping in the adiabatic representation including arbitrary couplings

09:30-09:50 ***Coffee break***

09:50-10:10 **Matthew Mills (Manchester)**
Intramolecular Polarisable Multipolar Electrostatics from a Machine Learning Method

10:10-10:30 **Thibaut Very (Vandoeuvre-lès-Nancy)**
UV-VISIBLE spectra of ruthenium complexes in interaction with DNA

10:30-10:50 **Zlatko Brkljača (Zagreb)**
Conformational study of small peptides and its relation to circular dichroism spectroscopy

10:55-11:55 **Plenary Lecture: Kenneth M. Merz (Florida)**
How Good Do We Have to be to Solve the Protein Folding and Protein-ligand Scoring Problems?

11:55-14:00 ***Lunch & Posters***
Please remove your poster afterwards

PROGRAM

Tuesday, April 5th 2011

14:00-14:20	**Thilo Bauer (Erlangen)** The Method of Tunneling Currents
14:20-14:40	**Karmen Čondić-Jurkić (Zagreb)** New insights in protonation states of catalytic histidines in (6-4) photolyase
14:40-15:00	**Christopher Pfleger (Düsseldorf)** Robust and efficient analysis of biomacromolecular stability using ensembles of random network topologies
15:00-15:20	***Coffee break***
15:20-15:40	**Markus Mühlbacher (Erlangen)** LogP as an archetype for modern QSPR
15:40-16:00	**Fatmawati Adam (Malaysia)** Force field performance in recognition of solvent mediated polymorphism of 2,6-dihydroxybenzoic acid from toluene and chloroform solution
16:00-16:20	**Fredrick Robin Devadoss Victor Paul Raj (Konstanz)** Analysis and Visual Summarization of Molecular Dynamics
16:20-17:20	**Plenary Lecture: Jürgen Brickmann (Darmstadt)** 25 Years of Modelling Workshop: Old Questions - New Answers?
18:00	***Social Event: Bierkeller (Steinbach Bräu)***

PROGRAM

Wednesday, April 6th 2011

08:30-08:50 **Vedat Durmaz (Berlin)**
Multi-Mode Molecular Dynamics Simulation of the Chromatographic Elution Order of Hexabromocyclododecane Stereoisomers

08:50-09:10 **Rok Borštnar (Ljubljana)**
Inhibition mechanism of Monoamine Oxidase B

09:10-09:30 **Hannes Wallnoefer (Innsbruck)**
Flexibility controls Specificity of Snake Venom Metalloproteases

09:30-09:50 ***Coffee break***

09:50-10:10 **Maurus Schmid (Basel)**
Ligand Binding Study of Carbonic Anhydrase 2

10:10-10:30 **Susanne von Grafenstein (Innsbruck)**
Impact of Tetramerization on Neuraminidase Dynamics

10:30-10:50 **Virginie Martiny (Paris)**
Probing small-molecule binding to sulfotransferases: an in silico protocol to predict metabolism and inhibition

10:55-11:55 **Plenary Lecture: Emad Tajkhorshid (Illinois)**
Dynamical View of Energy Coupling Mechanisms in Active Membrane Transporters

11:55-13:50 ***Lunch***

13:50-14:10 **Julian Fuchs (Innsbruck)**
Side Chain Oxidation Modulates Phenylalanine Hydroxylase Activity

14:10-14:30 **Shailendra Asthana (Cagliari)**
Effects of point mutation on BVDV RdRp : An In-silico study

14:30-14:50 ***Coffee break***

14:50-15:10 **Olujide Olubiyi (Jülich)**
Effects of an amyloid-inhibiting D-peptide on the conformations of the Alzheimer's peptide

15:10-15:30 **Piotr Setny (München)**
Hydration in discrete water - mean field, cellular automata based solvent model for calculating hydration free energies

15:30-15:50 **Nadine Homeyer (Düsseldorf)**
Enabling medium- to high-throughput free energy calculations with the AMBER suite

16:00 ***Poster & Lecture awards***

POSTERS

P01 **Ali Alizadeh (Tehran)**
Charge Configuration and its effect on Permeation through Carbon Nanotube

P02 **Shailendra Asthana (Cagliari)**
Effects of point mutation on BVDV RdRp : An In-silico study

P03 **Frank Beierlein (Erlangen)**
A Simple QM/MM Approach for Capturing Polarization Effects in Protein-Ligand Binding Free Energy Calculations

P04 **Rok Borštnar (Ljubljana)**
Calculations of pKa and Free Energies of Complexes

P05 **Alexander Bujotzek (Berlin)**
Designing molecular spacers for multivalent ligands by modeling and simulation methods

P06 **Luca Carlino (Halle)**
Structure-Based Design of Histone Demethylase Inhibitors

P07 **Anna Katharina Dehof (Saarbrücken)**
The Biochemical Algorithms Library (BALL) - Rapid Application Development in Structural Bioinformatics

P08 **Nedjoua Drici (Oran)**
Insight into structural properties of NCp7 proximal zinc finger: long-range electrostatic interactions effect on molecular dynamic simulations

P09 **Vedat Durmaz (Berlin)**
Multi-Mode Molecular Dynamics Simulation of the Chromatographic Elution Order of Hexabromocyclododecane Stereoisomers

P10 **Julian Fuchs (Innsbruck)**
Shape and Dynamics of Transcription Factor Binding Sites

P11 **Prashant Kumar Gupta (Basel)**
A molecular Dynamics study of water molecules with silica surface in chromatographic system

P12 **Anselm Horn (Erlangen)**
Aminopyrazole β-sheet Ligands – Design and Binding to Aβ42

P13 **Jing Zhou (Heidelberg)**
Structural and functional regulation of the Focal adhesion kinase by mechanical force

POSTERS

P14 **Christophe Jardin (Erlangen)**
Different sequence motifs of the Herpesvirus Tip protein mediate binding specificity for STAT transcription factors

P15 **Kristin Kassler (Erlangen)**
A Murine CD4 Derived Peptide Scaffold to Intervene gp120-CD4 Interaction

P16 **Simon Leis (Garching)**
Efficient Inclusion of Receptor Flexibility in grid-based Docking

P17 **Igor Levandovskiy (Kiev)**
Revisiting the Diels-Alder reaction: origin of selectivity and stability of endo adducts

P18 **Virginie Martiny (Paris)**
Probing small-molecule binding to sulfotransferases: an in silico protocol to predict metabolism and inhibition

P19 **Heike Meiselbach (Erlangen)**
Effect of the SH3-SH2 domain linker sequence on the structure of Hck kinase

P20 **Matthew Mills (Manchester)**
Intramolecular Polarisable Multipolar Electrostatics from a Machine Learning Method

P21 **Sabine Christel Mueller (Saarbrücken)**
Distributed Collaborative Molecular Modelling

P22 **Michaela Müller (Lübeck)**
Homology model of Abcc6 provides insight into the function of mutations causing cardiovascular phenotype

P23 **Stefan Nickels (Saarbrücken)**
Realtime Real-Time Ray Tracing in Molecular Visualization

P24 **Stefan Noha (Innsbruck)**
Development of a 3D pharmacophore model for inhibitors of NF-kB activation by combining structure-derived information and bias from a set of potent inhibitors

P25 **Annalisa Nuccitelli (Garching)**
A structure-based approach to rationally design chimeric proteins for a broad-spectrum vaccine against Group B Streptococcus infections.

POSTERS

P26 **Martin Pippel (Merseburg)**
ParaDockS - An Open Source Framework for Molecular Docking

P27 **Kristyna Pluhackova (Erlangen)**
Structure prediction of antimicrobial peptide Melectin in membrane mimicking environment

P28 **Susruta Samanta (Bremen)**
Interaction of Polyethylene Oxide and Polypropylene Oxide with Biological Interfaces

P29 **Avik Sanyal (Heidelberg)**
Accurate charges for transition metals in Molecular Mechanics

P30 **Sarah Schaefer (Halle)**
3D QSAR of substrates of the human H+/amino acid transporter PAT1

P31 **Michael Scharfe (Halle)**
Discovery of novel inhibitors for mono-ADP-ribosylating toxins

P32 **Sebastian Schenker (Erlangen)**
Silicon cation catalyzed (3+2)-Cycloadditions: A joint experimental and computational study

P33 **Sabine Schweizer (Freising)**
Structural Basis of Drug Resistance of Hepatitis C Virus Serine Protease Variants

P34 **Dmitriy Sharapa (Kiev)**
Polysubstituted derivates of pentacyclo-[6.3.0.02, 6.03,10.05,9]undecane

P35 **Inna Slynko (Halle)**
Homology Modeling and Docking Studies of PRK1 Kinase

P36 **Andrea Strasser (Regensburg)**
Distinct interactions between the human adrenergic β2 receptor and Gαs - an in silico study

P37 **Joachim Stump (Erlangen)**
Computational analysis of the conformational stability and receptor binding properties of glycoprotein D of herpes simplex virus-1

POSTERS

P38 **Jennifer Szczesny (Halle)**
The Catalytic Mechanisms of Sesquiterpene Formation in Zea Mays Prenylating Enzymes

P39 **Ozlem Ulucan (Saarbrücken)**
The Role of PIF-Pocket in Modulation of PDK1 Dynamics

P40 **Manisha Vekaria (Cambridge)**
Predicted surface structure and crystal growth mechanism of a natural zeolite

P41 **Thibaut Very (Vandoeuvre-lès-Nancy)**
UV-VISIBLE spectra of ruthenium complexes in interaction with DNA

P42 **Fredrick Robin Devadoss Victor Paul Raj (Konstanz)**
Analysis of Molecular Dynamics Simulation - For Small Polypeptides and Proteins

P43 **Susanne von Grafenstein (Innsbruck)**
Molecular Dynamics Simulations of Neuraminidase - Subtype N1

P44 **Hannes Wallnoefer (Innsbruck)**
Water Molecules Control Protein Structure and Ligand Affinity to fXa

P45 **Marcel Youmbi Foka (Erlangen)**
Comparative Study of two Classification Algorithms for the Prediction of Drug-induced Phospholipidosis

P46 **Vasilina Zayats (Nove Hrady)**
Structure and functions of transient receptor potential channel TRPA1

P47 **Wang Zhi (Cambridge)**
P-glycoprotein Substrate Models Using Support Vector Machines Based on a Comprehensive Dataset

P48 **Rasoul Nasiri (Tehran)**
Theoretical Studies on the Thermodynamics and Kinetics of the Lysine-Arginine Cross-Links Derived from α-Oxoaldehydes: A New Mechanism for Glucosepane Formation

All poster abstracts can be found on the conference website: http://www.chemie.uni-erlangen.de/ccc/conference/mmws11

LECTURES

On the Applicability of Normal Modes in Small-Molecule Docking

Matthias Dietzen[1], Elena Zotenko[2], Andreas Hildebrandt[3], Thomas Lengauer[1]

[1]Max-Planck-Institut für Informatik Saarbrücken, [2]Garvan Institute of Medical Research Sydney, [3]Johannes-Gutenberg-Universität Mainz

Incorporating protein backbone flexibility into protein-ligand docking is still a challenging problem in computer-aided drug design. In related fields, normal mode analysis (NMA) has become increasingly popular as it is able to determine the collective motions of a biological system. Its application areas range from the prediction of protein flexibility over the determination of protein domains and the guidance of MD simulations along the predicted collective motions to the fitting of proteins into electron density maps.

While incorporating normal modes from coarse-grained models into macromolecular docking has become a popular approach, the question whether they can also be useful in predicting the conformational changes observed upon small-molecule binding has only been addressed in some case studies [1, 2] . However, the interfaces for binding a macromolecule are usually much larger than those for binding a small molecule, a fact that requires a more detailed investigation.

We therefore have performed a large-scale study on the applicability of NMA in small-molecule docking by establishing a best-case scenario as follows. Using normal modes, we have generated intermediate structures from apo/holo pairs of the Astex Diverse [3] and Non-Native Sets [4] by projecting the conformational difference between both partners onto normal mode subsets of increasing size. The resulting C_α traces optimally reproduce the holo conformation w.r.t. the given normal mode subspace. Subsequently, the all-atom structures have been reconstructed and energy-minimized, C_α atoms were kept fixed. These structures were then docked using AutoDock [5] , GOLD [6] , and FlexX [7] to assess how the docking performance changes over a series of increasingly well reproduced holo structures and to estimate the number of modes required to sufficiently reproduce the conformational change induced by the ligand.

The results of our study indicate that even for such a best-case scenario, the use of normal mode analysis in small-molecule docking is restricted and that a general rule on how many modes to use might not exist or at least not be easy to find.

[1] C. N. Cavasotto, J. A. Kovacs, R. A. Abagyan, *J Am Chem Soc*, **2005**, *127*, 9632-9640.
[2] A. May, M. Zacharias, *J Med Chem,* **2008**, *51*,3499-3506.
[3] J. W. Nissink, C. Murray, M. Hartshorn, M. L. Verdonk, J. C. Cole, R. Taylor, *Proteins*, **2002**, *49*, 457-471
[4] M. L. Verdonk, P. N. Mortensen R. J. Hall, M. J. Hartshorn, C. W. Murray, *J Chem Inf Model*, **2008**, *48*, 2214-225 .
[5] D. S. Goodsell, G. M. Morris, A. J. Olson, *J Mol Recognit,* **1996**, *9,* 1-5.
[6] G. Jones, P. Willett, R. C. Glen, A. R. Leach, R. Taylor, *J Mol Biol,* **1997**, *267*,727-748.
[7] M. Rarey, B. Kramer, T. Lengauer, G. Klebe, *J Mol Biol,* **1996**, *261*, 470-489.

Efficient Inclusion of Receptor Flexibility in grid-based Docking

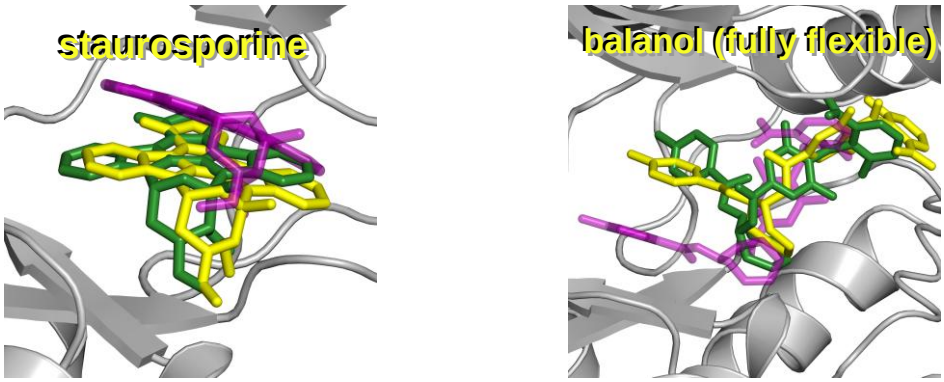
Simon Leis and Martin Zacharias

Physik Department T38, Technische Universität München, 85748 Garching, Germany

Receptor flexibility is by now considered an essential component for successful protein-ligand docking but still marks a major computational challenge [1]. Docking programs such as AutoDock [2] employ a grid-based potential representing the receptor and allow efficient docking of flexible ligands. However, global receptor flexibility is not yet properly accounted for in such methods.

Here, we present a new approach [3] to efficiently include receptor flexibility by combining normal mode calculations [4] with grid-based energy calculations in AutoDock. Similar to many other proteins, the Protein Kinase A (PKA) undergoes global structural changes upon inhibitor binding which makes it an especially challenging docking target. It serves as test case for our method. Docking ligands to apoPKA using standard AutoDock (rigid receptor) returns ligand placements that differ strongly from experiment (see figure below: compare stick representations in magenta from rigid docking to apoPKA with yellow stick models showing the placement in the experimental complex). In contrast, inclusion of normal mode based receptor flexibility calculated for the apoPKA structure yields significantly better docking results (indicated in green).

The computational effort to calculate elastic network based normal modes is negligible compared to AutoDock's genetic algorithm runtime, hence, a significant improvement of docking results at small computational cost is accomplished. The computational method and several applications will be presented.



[1] J.D. Durrant and J.A. McCammon , *Curr. Opin. Pharmacol.*, **2010**, *10*, 770-774.
[2] G.M. Morris, R. Huey, W. Lindstrom, M.F. Sanner, R.K. Belew, D.S. Goodsell and A.J. Olson, *J. Comput. Chem.*, **2009**, *30(16)*, 2785-2791.
[3] S. Leis and M. Zacharias, *in preparation*
[4] K. Hinsen, *Proteins*, **1998**, *33*, 417-429.

Computational And Experimental Studies Of New Cage Compounds - Potential Antiviral Drugs

Alexander V. Gayday[1], Igor A. Levandovskiy[1], Tatyana E. Shubina[2]

[1]National Technical University of Ukraine, Dept. of Organic Chemistry, Pr. Pobedy 37, 03056 Kiev, Ukraine, lia198@bigmir.net

[2]Computer-Chemie-Centrum and Interdisciplinary Center for Molecular Materials, FAU Erlangen, Naegelsbachstr 25, 91052, Erlangen, Germany;

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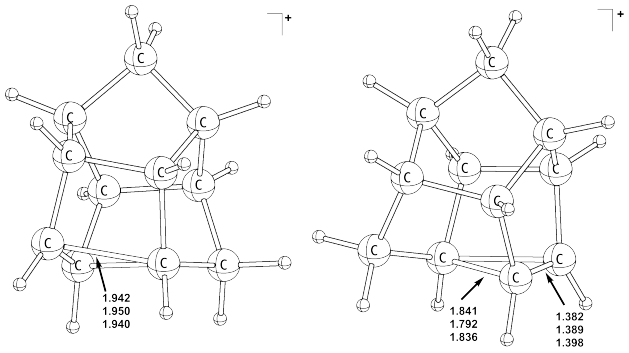
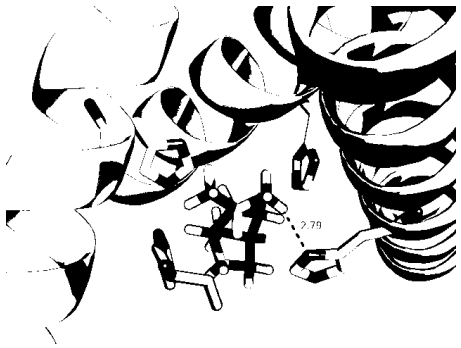
The new strains of influenza A virus are resistant to common antiviral drugs Amantadine and Rimantadine, which are blockers of the viral M2-proton channel. The docking studies have shown that better inhibitors of this channel are the substances containing cage fragment separated from polar residue by one carbon atom. [1] We have suggested to change the lipophilic hydrocarbon part from adamantane to D_3-trishomocubane. For preparing such analogues of rimantadine starting compound must be the trishomocubane carboxylic acid.



An efficient synthetic strategy to obtain 1-substituted-D_3-trishomocubane is described. B3PW91/6–31G(d,p) and MP2/cc–pVDZ calculations offer plausible explanation of the reaction mechanism.

Figure 1. Geometry of equivalent cations, (bond lengths in Å, B3PW91/6–31G(d) (first entry), B3PW91/6–311+G(d,p) (second entry) and MP2/cc–pVDZ (third entry)).

Binding of blockers to the Influenza A M2 ion-channel is studied using automated docking calculations. Our study present various binding sites for the studied cage compounds within the TM-M2 region.[1]



Our study suggests that such compounds block the M2 ion channel by binding to the His^{37} residue. The alkane cage fits into a pocket formed by Trp^{41} residue, while the hydrogen bond is formed between hydrogen atom of the NH_3^+ group and the nitrogen of histidine residue (Figure 2).

Figure 2. A close view at the compound docked into M2 channel. Only three chains of M2 protein (cartoon) and Histidine-37 residues are shown.

[1] A.V. Gaydai, I.A. Levandovskiy, K.G. Byler, T.E. Shubina *Lecture notes in Computer Science* - Vol. 5102, Springer, **2008**, pp. 360-368.
[2] D.I. Sharapa, A.V. Gayday, A.G. Mitlenko, I.A. Levandovskiy, T.E. Shubina, *EJOC*, **2011**, *ASAP*.

Multipolar Force Fields in Chemical and Biological Simulations

Markus Meuwly

Department of Physical Chemistry, University of Basel, Klingelbergstrasse 60, 4056 Basel, Switzerland

Conventional force fields use point charges to represent the electrostatics between interacting sites. Such a procedure is economical but for certain applications the accuracy is not sufficient. In particular for dynamics in spatially constrained environments anisotropic components of the interactions become important. Also, for small molecules with vanishing low-order multipoles, inclusion of higher multipoles becomes mandatory. In my presentation I will discuss applications of multipolar force fields to infrared spectroscopy and vibrational relaxation. Implications for the interpretation of experimental data will also be discussed.

Reliably and repeatably predicting free energies by combining MM-PBSA with LES

Richard T. Bradshaw, Pietro G.A. Aronica, Robin J. Leatherbarrow, Edward W. Tate & Ian R. Gould

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Calculating free energies of binding for protein-protein interactions accurately and reliably remains a challenging goal for biomolecular simulations. The MM-PB/GBSA approaches are widely used to predict and rank relative binding free energies ($\Delta\Delta G$) for complexes and their mutants. However, the accuracy and repeatability of their predictions is plagued by inherent difficulties with molecular dynamics (MD) – how can we be sure of generating converged free energy estimates and sampling experimentally relevant dynamics on the MD timescale?

Previous work in our group [1] and by others [2] has highlighted the use of multiple independent trajectories in improving precision of $\Delta\Delta G$ estimates, as well as the potential advantages of using post-process alanine scanning for cancellation of errors between native and mutant trajectories. However, post-process alanine scanning is not suitable in cases where mutation may induce local structural changes in the protein. Therefore, we propose an alternative approach to generating mutant dynamics using a heterogeneous form of Locally Enhanced Sampling (LES).

We perform LES simulations combining copies of native and mutant structures simultaneously, then extract the trajectories of native and mutant structures separately and calculate $\Delta\Delta G$. This combines the cancellation of errors present in post-process alanine scanning with allowances for small local rearrangements on residue mutation, potentially far better replicating the experimental dynamics. In addition, the size of the LES region (in which we allow local differences between native and mutant) is entirely flexible, and likewise the protocol also allows for mutations to residues other than alanine.

Preliminary results have shown good agreement with experimental data for a variety of mutations, hence we are currently extending the protocol to situations where traditional MM-PB/GBSA or post-process alanine scanning has failed to predict $\Delta\Delta G$s correctly.

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A Pipeline for the training of NMR chemical shift prediction models

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NMR chemical shift prediction plays an important role in many applications in computational biology [1]. Among others, structure determination, structure optimization, and the scoring of docking results can profit from efficient and accurate chemical shift estimation from a three-dimensional model of the molecule under consideration. The development of novel prediction techniques is a challenging task. The required information is spread over several databases and stored in hard-to-parse file formats which sometimes contain serious errors. In addition, the computation of physical terms or of molecular features for a heuristic approach requires complex molecular data structures and algorithms.

Here, we present a pipeline for developing hybrid NMR chemical shift prediction methods that combine physical terms – approximations to quantum mechanical effects – with a statistical model. The pipeline allows the simple import of data from diverse sources, such as the BMRB and the PDB. Several semi-classical terms for shift prediction are implemented and readily available. As of now, we include random coil contributions, aromatic ring current effects, electric field contributions, and hydrogen bonding effects. The feature set for the training of the statistical term encompasses sequential, structural (angles, surface, and density), force-field based, and experimental properties. All features are computed using our open source library BALL [2], and can be easily extended.

For the statistical contribution we propose a random forest model which has demonstrated in our experiments to yield very accurate and stable results. In general, however, the pipeline is model-agnostic and can be used with any regression technique implemented in R.

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Water ordering around small hydrophobic solutes in electric fields

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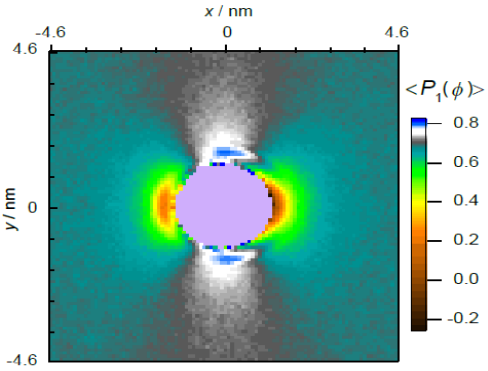
The hydrophobicity of an interface, droplet or a particle can be modulated by an external electric field in a process called electrowetting. [1] Such a change of surface characteristics allows for the regulation of macroscopic properties such as adhesion or friction in micro and nano-fluidics by the electric field. [2] The organization of water around hydrophobic objects, in the absence of an external field, has been studied extensively over the last decades. [3] However, the effect of the field on hydrophobic solvation is much less well understood.

In this contribution, we investigate the detailed structure of water around an idealized hydrophobic solute by means of extensive molecular dynamics simulations. We have used the data from these simulations to evaluate the total solute-solvent correlation function, which includes the orientational degrees of freedom of the solvent. Under the influence of the external field, it is particularly instructive to examine the correlations in the meridian planes of the solute. Similarly revealing is the analogous projection of the water dipoles in the direction of the field (see picture). We find an interesting competition between the optimal orientation of water with respect to the field and the solute particle. On one hand, this results two low-density regions around the +x and –*x* poles of the particle, with the depletion being more pronounced on the +*x* side. On the other hand, the symmetrically placed high-density regions on the +y and –*y* poles appear to have very long-ranged ramifications.



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LECTURES

MONDAY

Efficient Computational Methods for Transition Metal Complexes: Computational Characterization of a Hydrogen-Bonded Bidentate Catalyst

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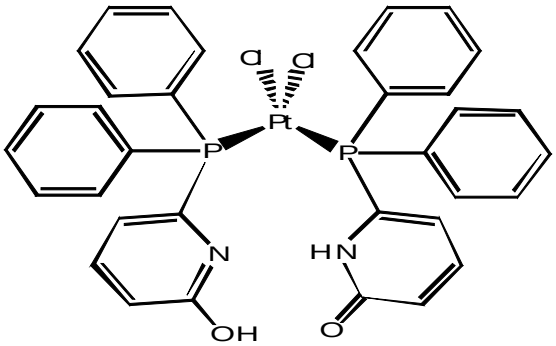
Rapid calculation of the structures and energies of transition metal complexes is desirable for understanding and optimizing catalysts. Here we present results from a molecular mechanics (MM) based strategy for this purpose. The VALBOND force field [1] developed by Landis *et al.* has been implemented into CHARMM and extended into VALBOND-TRANS by adding terms that account for the trans influence of ligands on bond lengths and relative energies.[2] This approach can also be combined with other force field methods developed in our group, for example molecular mechanics with proton transfer (MMPT). [3]



$Pt[Cl_2(6\text{-}DPPon)_2]$ is among a series of homogeneous catalysts proposed, characterized and tested by Breit *et al.* [4], which constitute the self-assembly of monodentate ligands through hydrogen bonding and provide high activity and regioselectivity in hydroformylation. Here we show that MM force field are suitable for a detailed atomistic characterization of structures and energetics of such complexes. The results demonstrate that force field-based methods are quantitative compared to experimental and other computational methods while they are several orders of magnitudes faster. Nanosecond molecular dynamics (MD) simulations of this Platinum catalyst were carried out in both gas phase and explicit solvation. Infrared, UV/Vis and NMR spectra were computed from MD trajectories and compared with experimental measurement, and the hydrogen bonding situation in the complex is studied. Combining force field methods with *ab initio* calculations and experimental data, modes of action of cis-$Pt[Cl_2(6\text{-}DPPon)_2]$ can be characterized in atomistic detail. [5, 6]

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Modeling Molecular Electronic Properties with Semiempirical UNO-CAS

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The abbreviation UNO–CAS stands for **U**nrestricted **N**atural **O**rbitals (UNOs, **U**) – **C**omplete **A**ctive **S**pace. It is defined as full configuration interaction performed in the active space. The active space is readily defined as that of the UNOs with significant fractional occupations (between 0.02 and 1.98). The method was originally proposed by J. M. Bofill and P. Pulay as an *ab-initio* method and an inexpensive alternative to the CAS–SCF (complete active space–self-consistent field) method. [1] UNOs together with their occupation numbers **σ** can be obtained *via* diagonalization of the total UHF density matrix $\mathbf{P}^T$ (sum of α- and β-density matrices from UHF calculations), *i.e.* solving the eigenvalue problem: [2]

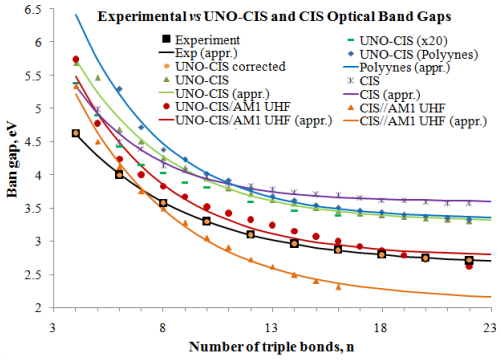
$$\mathbf{S}^{1/2}\mathbf{P}^T\mathbf{S}^{1/2}(\mathbf{S}^{1/2}\mathbf{U}) = (\mathbf{S}^{1/2}\mathbf{U})\boldsymbol{\sigma} \quad (1)$$

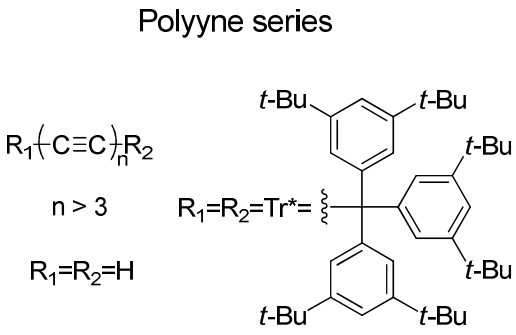
where the UNOs are the eigenvectors and the occupations are the eigenvalues of $\mathbf{P}^T$ and **S** is the atomic orbital (AO) overlap matrix. If the latter is unity, equation (1) is simplified to: [2]

$$\mathbf{P}^T\mathbf{U} = \mathbf{U}\boldsymbol{\sigma} \quad (2)$$

Here we extend formalism to obtain the semiempirical UNO–CAS method with the additional possibility of performing configuration interaction singles (CIS) as well as CI singles and doubles (CISD) in the active space, which we call semiempirical UNO–CIS and UNO–CISD, respectively. The UNO–CIS method is obviously computationally much cheaper and allows us to perform calculations for relatively large molecules with active spaces that include more than a hundred orbitals.

For instance, this method can predict the optical band gaps (E_g) of the substituted polyyne series in good agreement with available experimental data [3]. The choice of orbitals to be used in conventional semiempirical CI calculations is not obvious and it can be a significant problem to determine a reasonable number of orbitals as the number of triple bonds in the polyyne series changes. However, UNO–CIS allows this number to be determined automatically. Moreover, UNO–CIS band gaps are generally in better agreement with experiment than those calculated using conventional semiempirical CIS with the same number of orbitals. Thus, UNO–CAS can be used successfully to predict E_g values for unknown species and therefore to model new materials especially in the field of nanoelectronics.





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SHARC – *ab initio* molecular dynamics with surface hopping in the adiabatic representation including arbitrary couplings

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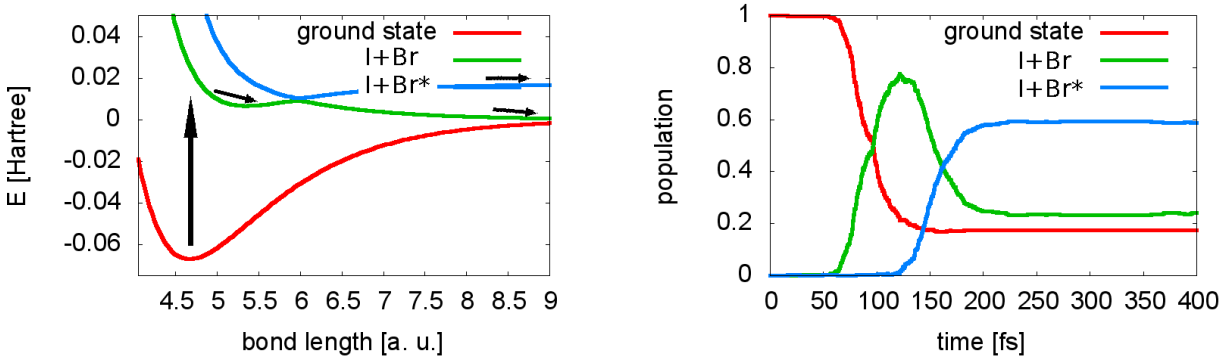
The **s**urface-**h**opping-in-**a**diabatic-**r**epresentation-including-arbitrary-**c**ouplings (SHARC) method is presented. This semiclassical molecular dynamics method allows for the inclusion of arbitrary couplings like spin-orbit coupling (SOC) or laser field induced couplings into molecular dynamical investigations. For this purpose, the surface hopping methodology [1] is extended and the couplings are incorporated into the system's Hamiltonian via a unitary transformation.



The method is tested in an analytically fitted 3-state system of IBr [2] (see left picture). Due to SOC there are two different dissociation channels, leading to I + Br($^2P_{3/2}$) (ground state) and I + Br*($^2P_{1/2}$) (excited Br) products.

To demonstrate the possibility of treating different couplings at the same time with high accuracy, the dissociation of IBr (including SOC) after excitation with a Gaussian shaped laser pulse (including field induced couplings) is investigated. The right picture shows, how the population of the different states changes with time due to the different couplings that affect the system's dynamics. These results, obtained from an ensemble of independent trajectories, are in good agreement with exact quantum dynamical calculations [3].

In contrast to quantum dynamics, within molecular dynamical calculations, the knowledge of the complete potential energy surface is not necessary a priori. Thus, the calculation of the required quantum mechanical properties can be done on the fly at the relevant geometries, allowing for the modeling of large and complex systems with many degrees of freedom.

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Intramolecular Polarisable Multipolar Electrostatics from a Machine Learning Method

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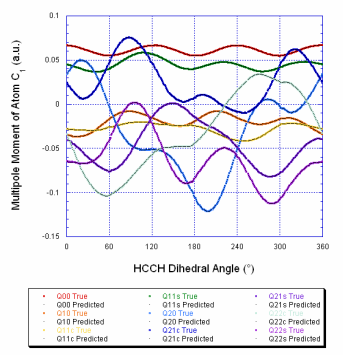
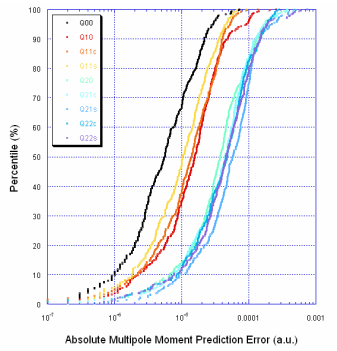
Manchester Interdisciplinary Biocentre, University of Manchester





Molecular mechanics methods are ubiquitous in the computational study of chemical problems. Evaluation of the energy of a system with these methods is often many orders of magnitude less computationally expensive than *ab initio* calculation of the same property. However, application to biological systems highlights several shortcomings [1]. In particular, such systems tend to be highly polar leading to difficulty in modeling electrostatic interactions with typical simple expressions. The replacement of inherently limited point charges by a multipolar energy expression relieves this problem by providing a more realistic description of the charge density. In addition, we have applied a machine learning method called Kriging [2] in conjunction with the atomic partitioning at the heart of Quantum Chemical Topology [3,4] to capture the changes in multipole moments with nuclear configuration, that is, the intra-atomic polarisation. The proposed method retains the speed advantage of force field methods over *ab initio* calculations but provides a far more accurate electrostatic picture. Applied to the molecule ethanol as a pilot system, the method produces very accurate results for both the multipole moments and the total molecular 1-4 and higher electrostatic interaction energy over a full range of conformations, with a maximum absolute energy error for any conformation below 0.01 kJmol^{-1}. Extension of the method to other classes of molecules is straightforward. An important advantage of Kriging is that the method remains accurate for systems with a large number of atomic coordinates describing the nuclear configuration. Work towards a general force field for proteins that employs the described methodology is underway.

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UV-VISIBLE spectra of ruthenium complexes in interaction with DNA

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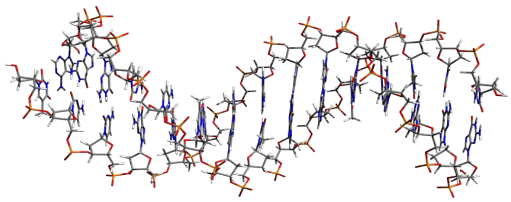

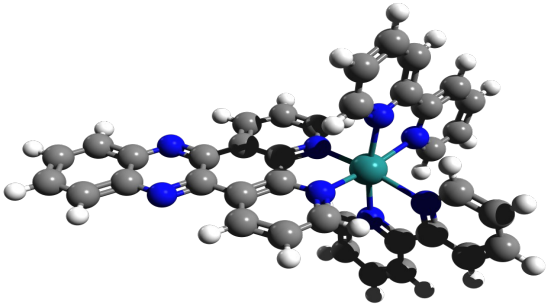

Transition metal complexes are widely used and the coverage of applications is quite broad. In medicine domain, and particularly concerning treatments of diseases like cancer, platinum complex known as cisplatin is given daily. However, the side effects felt while taking this drug are strong. In order to reduce side effects, research has turned toward other transition metal, showing less cytotoxicity, like ruthenium.[1] Combined with polypyridyl ligands, it show interesting photoluminescence properties and can be used as a light probe of the interaction with DNA.

Here we present a combined QM:MM study of the interaction between DNA and a ruthenium complex : [dipyridophenazino,bisbipyridino,ruthenium]$^{2+}$. This complex exhibit fluorescence while interacting with DNA whereas this fluorescence is quenched in aqueous media.[2] Firstly, we carried out MM minimizations on a system made of a 15 base pairs B-DNA, the complex intercalated into the double strand and a cylinder of water molecules, in order to see which configurations are more likely to happen. These calculations are being followed by QM:MM optimizations and finally TDDFT calculations to retrieve UV-Visible absorption spectra. We show the effect of intercalation into DNA for the complex.

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CONFORMATIONAL STUDY OF SMALL PEPTIDES AND ITS RELATION TO CIRCULAR DICHROISM SPECTROSCOPY

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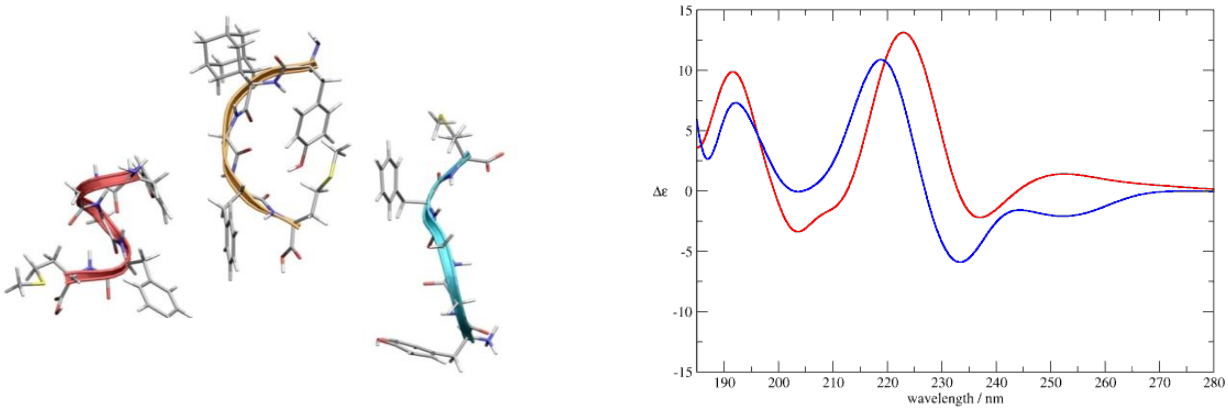

Opioid peptides are known to be associated with many physiological features such as pain mediation, opiate dependence, and euphoria. [1] They are also known to possess affinity for several distinct receptors, implying an ability to assume different shapes for different purposes. Particularly important in this respect is the anti-cancer activity of Opioid Growth Factor (OGF). Improved effects have been seen for its unnatural analogues, which have been proposed to have a structural origin. [2] Using replica exchange molecular dynamics, we have investigated the structural preferences of these peptides. The simulations were performed in explicit trifluoroethanol, as a prototypical low polarity environment. In order to provide a direct link with experiment, circular dichroism spectra of the peptides were calculated using a QM/MM approach in which the peptide was treated quantum mechanically, while the effect of the solvent was included classically.

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How Good Do We Have to be to Solve the Protein Folding and Protein-ligand Scoring Problems?

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Computational Chemistry/Biology is now a well-established field with numerous significant successes to show for several decades of effort. Nonetheless, several challenges remain both from the computational/theoretical and experimental perspective. This talk will touch on several of these challenges and suggest ways in which to overcome them in the coming years. In particular, we will touch on the establishment of error bounds in computational prediction of the free energy of binding of a ligand for a protein target and the folding free energy of a protein and how this affects the outcome of absolute *versus* relative energy computations. Through the formation of probability distribution functions based on CCSD(T)/CBS reference energies we show that computed interaction energies, by multiple methods, typically have significant systematic as well as random errors. Detailed analyses of NDDO based methods, force fields, density functional theory, Hartree-Fock and correlated methods will be presented. Based on these insights we will discuss what future research directions will have the most impact in ultimately leading to the solution of the *ab initio* protein folding and *in silico* drug design problems.

The Method of Tunneling Currents

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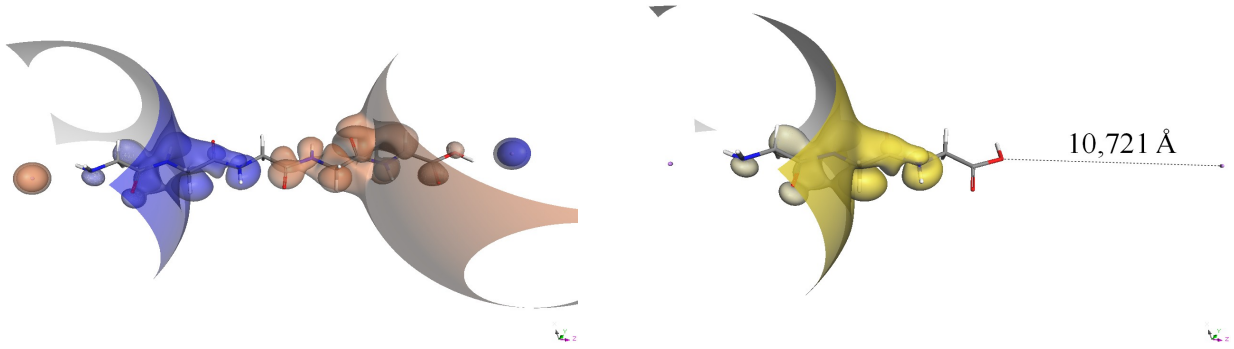

Transition states of electron transfer reactions are stationary states. The description as stationary states allows to apply the Born-Oppenheimer-approximation to the system of interest. Therefore in a series of UHF energy calculations the transition state of an electron transfer reaction can eventually be found by varying an external point charge that acts on the system [1]. The external pointcharge simulates effects of a dipolar medium such as rotations of water molecules on the electronic energy of the redox centers. If two different redox states with same electronic energy can be found, one has found the transition state of the electron transfer reaction. In the transition state an electron can be transferred to the other redox center via tunneling [2]. An analysis of the tunneling process gives insight into the electron transfer reactivity of the system, that means one is able to identify the parts of a system that are (un)necessary for the electron transfer.

By implementing respective formulas [2][3], we will be able to calculate and visualize the vector field of the tunneling flux as well as the electronic coupling of donor- and acceptor states.

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New insights in protonation states of the catalytic histidines in (6-4) photolyase

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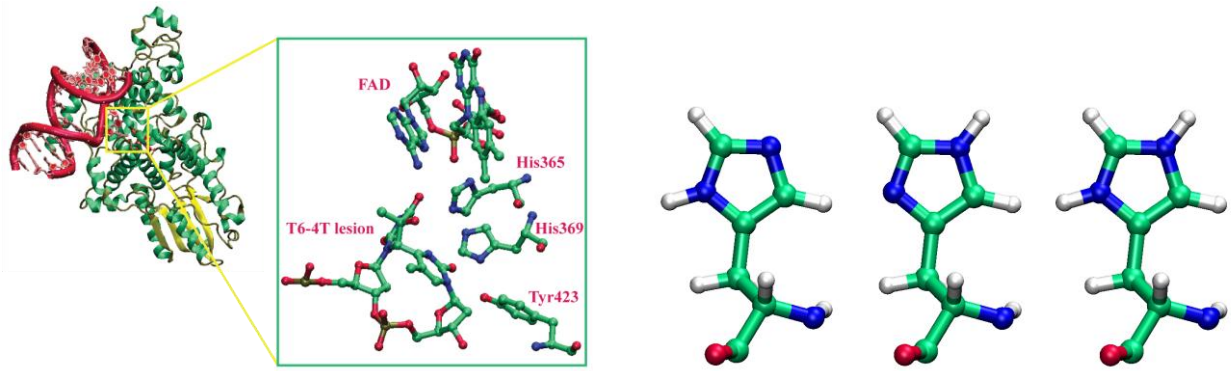
[2]Excellence Cluster: Engineering of Advanced Materials, University of Erlangen-Nürnberg, Erlangen, Germany
[3]Department of Chemistry, Ludwig-Maximilians Universität, München, Germany



Exposure of cells to UV radiation leads to the formation of different lesions in DNA strands, one of which is a pyrimidine-pyrimidone dimer known as the (6-4) DNA lesion. (6-4) photolyases are enzymes that, together with FAD, are capable of repairing the dimer and regenerating the original monomers. Since the resolution of a (6-4) photolyase crystal structure,[1] several different mechanisms have been proposed. Nevertheless, open questions still remain.[2] It has been established that two active-site histidines and a nearby tyrosine residue are key residues in catalysis. To determine the role of the histidines, which are presumed to act as an acid-base pair, it is vital to assign their protonation states correctly. The measured hyperfine couplings of selected protons of the $FADH^{\bullet}$ radical, obtained from an EPR/ENDOR study, have been previously used as evidence in the protonation-state discussion.[3] Our QM/MM calculations of these couplings, however, suggest that they are not the most appropriate probe in this context. To further investigate the effect of the environment on the active-site histidines, their pK_a values were estimated with several approaches based on the Poisson-Boltzmann equation. Finally, a series of explicit-solvent molecular dynamics simulation were performed for each of the 9 combinations of protonation states for two adjacent histidines, with different oxidation states of the FAD cofactor. A consistent picture of the active form of the catalytic histidines emerges from a combination of the three applied methodologies.

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Robust and efficient analysis of biomacromolecular stability using ensembles of random network topologies

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Biomacromolecules require a balance of flexibility and rigidity to achieve their diverse functional roles. Hence, it is desirable to have a precise knowledge about what can move and how. The flexibility for a given biomacromolecule can be analyzed within a few seconds by a graph theory-based approach as implemented in the FIRST program (*F*loppy *I*nclusions and *R*igid *S*ubstructure *T*opography)[1]. Previous studies have demonstrated that the approach is sensitive with respect to the structural information used as input [2,3]. This sensitivity problem can be overcome by analyzing an *ensemble of network topologies* rather than a single structure network. To do so, MD-generated conformations were used so far. This way, however, the efficiency of the FIRST approach is lost.

Here, we will present a more efficient alternative where an ensemble of network topologies is generated by fluctuating non-covalent constraints in a constraint network derived from a single input structure, with hydrogen bonds, salt-bridges, and hydrophobic tethers varied. This approach has been implemented into the Constraint Network Analysis (CNA) program package developed in our group. The CNA program functions as a front-end to the FIRST software and allows to I) set up a variety of constraint network representations for rigidity analysis, II) process the results obtained from FIRST, and III) calculate different indices for characterizing macroscopic and microscopic stability in biomacromolecules.

The approach of fluctuating networks was validated on a dataset of 38 lysozyme crystal structures with high structural quality as well as on four MD trajectories of lysozyme[4]. Remarkably, in almost all cases of the 38 lysozyme crystal structures, the predicted flexibility/rigidity characteristics are in good agreement with results obtained from ensembles of network topologies derived from the four MD trajectories. Each calculation requires less than 5 h of computing time on a standard workstation computer. The approach shall thus be valuable when it comes to investigating many proteins, e.g. in the case of analyzing the effect of mutations on protein stability.

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LogP as an Archetype for modern QSPR

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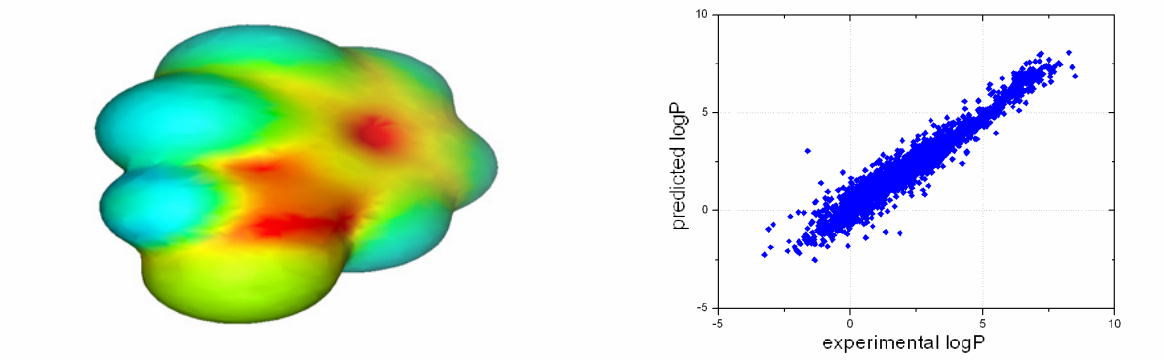
LogP, the distribution coefficient between 1-octanol and water, is a well established and widely used measure for lipophilicity. Due to its immense impact on drug design a large number of *in silico* predictions have been developed up to now. Here we present a new approach for logP modeling, as well as a novel application for conformation sensitive logP predictions.

Binned surface-integral models and the descriptors used to construct them are clearly well able to predict logP as accurately as is allowed by the experimental data [1]. Based on the inconsistency of the used dataset (N=11590), we estimate a maximum possible accuracy given by the root mean squared error (RMSE) of 0.48 logP units.

In agreement with this limitation we were able to construct quantitative structure property relationship (QSPR) models with an RMSE of approximately 0.50 log units, using bagged multiple linear regression. These models proved to be extremely robust with respect to rigorous validation (bootstrapping and external validation).

Additionally, logP also embraces the ability of a compound to form hydrophobic interactions. Following this assumption, we used our logP predictions to estimate protein-ligand binding affinities for the Astex validation set [2]. Please note, that in this context the conformation is already given by the crystal-structure. Thus we used single point calculations (instead of full optimization) and calculated the atomic contributions to logP. We summed up all contributions for contact atoms (distance to protein < 4.5 A) to give an estimate for the ability to form hydrophobic interactions.

We analyzed the logP contributions with respect to binding affinities (given by pKi). Without any further fitting this already suggests to be a good estimate for binding affinity. Summarizing, we were able to show that conformation-sensitive logP prediction can be used to estimate binding affinity. In contrast to other scoring functions it is neither hypothesis driven, nor fitted to experimental binding affinity data.



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Force field performance in recognition of solvent mediated polymorphism of 2, 6-dihydroxybenzoic acid from toluene and chloroform solution

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2, 6-Dihydroxybenzoic acid has been evaluated as an active pharmaceutical ingredient, for example in the treatment of tumors, and is employed, commonly, as a reagent in the synthesis of pharmaceutical materials especially antipyretic, analgesic and antirheumatism agents. In this molecular modelling study, two polymorphic forms of 2, 6-Dihydroxybenzoic acid were investigated in two different solvent environments to assess the effect of solvent type at same level of solution supersaturation, on the nature of the intermolecular hydrogen-bonding interactions. Experimentally it is found that, generally, Form I is crystallized from toluene while Form II is crystallized from chloroform solution[1]. Molecular dynamics (MD) techniques were applied to simulate the molecular recognition processes operating between solvent and solute molecules prior to nucleation and phase separation from solution. The MD simulations employed the computer program DLPOLY and the probabilities of finding specific intermolecular interactions in specific solvent environments were assessed by calculating radial distribution functions from the simulation trajectory files which initially equilibrated under NVE and followed by NPT ensembles. Dreiding[2] and OPLSAA performed well in simulating the liquid system such the pure solvent as the calculated densities, rdfs and diffusion in a good agreement to the theoretical values compared to COMPASS force field.

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Analysis and Visual Summarization of Molecular Dynamics

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Molecular Dynamics (MD) simulation is a standard technique used to study the dynamical properties of bio-molecules. The trajectories collected in a MD simulation consists of a very large file containing a serious of 'snap shots' over the simulation time. Analyzing these trajectories may take much longer time than the data generation and the conformational changes may range from small local variation to large displacement of entire domains. Standard parameter like root mean square deviation (RMSD) does not reveal the most interesting properties of the dynamics. Also, managing the large amount of data and presenting them in a comprehensive manner are the major challenges in the analysis part of the MD simulation.

To over come these problems, we use C-alpha torsion angle – pseudo dihedral angle defined by four successive C-alpha atoms [1]- as a parameter. The calculation of differences in C-alpha torsion angles between each steps help to identify the conformational changes without any bias. Hence, we use this approach to identify the local and global conformational changes during MD simulation. To handle the huge amount of data, we use KNIME [2], a user-friendly and comprehensive open-source data integration, processing, analysis and exploration platform.

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25 Years Molecular Modeling Workshop: Old Questions - New Answers?

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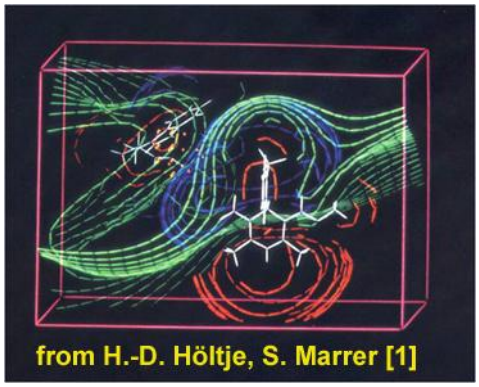
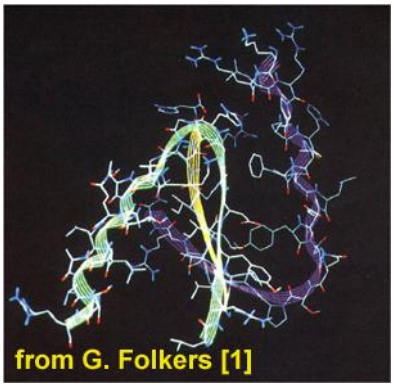
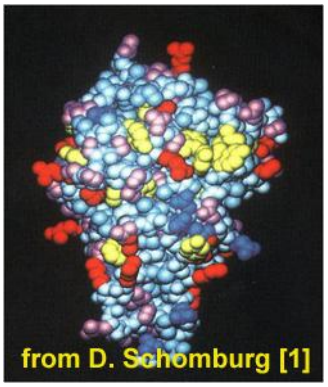
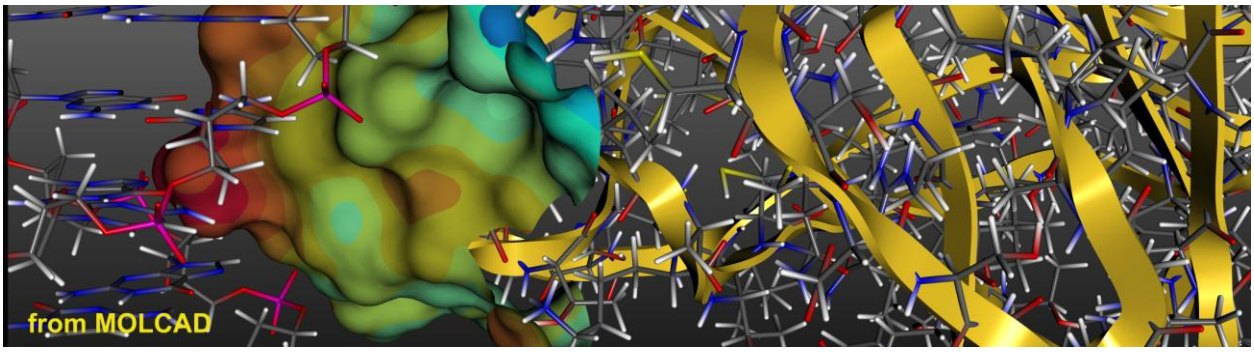
The first molecular modeling workshop took place in Darmstadt in 1987. The workshop was initiated and supported by the German Ministry of Science and Technology with the aim to bring together researcher from academia and industry from the field of computer aided molecular design. The background was a program of the German government directed towards the reduction of animal experiments in pharmaceutical research by alternative methods. Many scientist, well known in the field, contributed to this event. [1]







The basic questions have been the same as today: Industrial researcher mainly asked "How can computer aided methods be used in order to reduce the effort in the development process for new drugs?" while the questions from academia have been related to the understanding and the quantification of the molecular recognition process. The basic model scenario was crude and its visualisation and numerical treatment could only be handled with "super computers" with a capacity which is smaller than that of today´s laptops. The answers have been vague. The situation is much different today. According to Moore´s rule (computer capacity doubles roughly every two years) one may estimate a factor of about 10^4 to 10^5 in capacity. Moreover, there was a big step forward on the software side. Instead of crude models, we can use today sophisticated ones including quantum mechanical treatments and simulation techniques. Modern computer graphics techniques allows an effective real time man machine communication in the modeling and simulation business. Nevertheless, we are still far away from adequate answers to the old questions. Tim Clark formulated the situation of the modeling community as "Soothsayers or Scientists" [2]. The recent problems and some ideas for the future developments will be discussed in this contribution.



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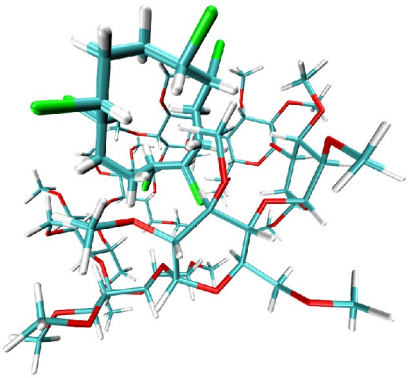
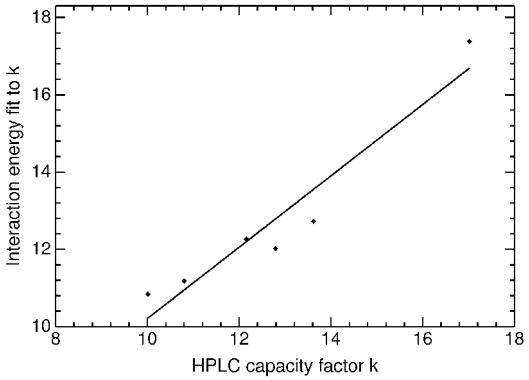
Multi-Mode Molecular Dynamics Simulation of the Chromatographic Elution Order of Hexabromocyclododecane Stereoisomers

Vedat Durmaz*, Marcus Weber*, Roland Becker**

*ZIB Zuse Institute Berlin, Department of Numerical Analysis and Modelling, Computational Molecular Design

**BAM Federal Institute for Materials Research and Testing, Department of Analytical Chemistry, Reference Materials





Liquid chromatographic separation of the six major diastereomers – three enantiomeric pairs – of the additive flame retardant hexabromocyclododecane (HBCD) has been studied by means of classical molecular mechanics with both explicit solvents water and acetonitrile. For this pupose, classical force field interaction energies with the entire surrounding were fit to experimental capacity factors derived from retention times of HPLC analysis. Since molecular dynamics simulations rarely provide considerable spatial rotations and conformational changes, high-temperature hybrid Monte-Carlo runs were performed with subsequent conjugate gradient minimizations in order to gain global minimum conformations serving as starting structures for multiple runs with differing initial binding modes in accordance with the icosahedron's symmetry. Besides, three strategies have been developed in order to determine the optimal binding mode. Using the small data set of HBCD, high squared coefficients have been computed of the correlation between optimal interaction energies coping with thermodynamic principles and experimental capacity factors with R^2=0.92 where enantiomeric separation was estimated exactly.

Inhibition mechanism of Monoamine Oxidase B

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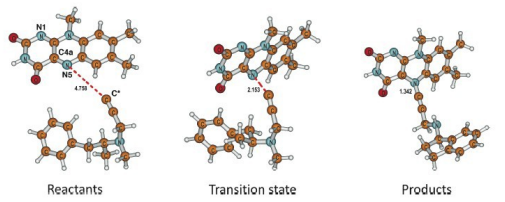
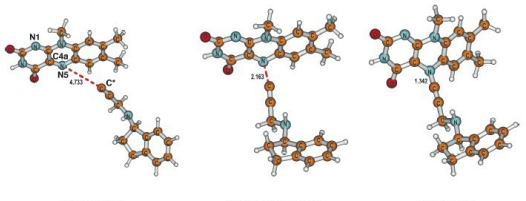
Monoamine oxidase (MAO) is an enzyme from the familly of flavoenzymes attached with its C-terminal end [1] to the outer mitochondrial membrane of brain, liver, intestinal, placental cells, and platelets. It is responsible for metabolism of important neurotransmiters serotonin, dopamine and norepinephrine, and it exists in two isozymic forms MAO-A and MAO-B. This two isozymic forms differ in selectivity to substrates and consequently to the inhibitors. MAO-A mainly metabolizes norepinephrine and serotonin. Inhibitors of MAO-A are used to elevate the norepinephrine and serotonin concentrations and thus improving the symptoms of depression. In contrast MAO-B is involved in metabolism of dopamine [2], a neurotransmitter involved in control of voluntary movement. Insufficient dopamine stimulation of the basal ganglia has been established to be a characteristic for Parkinson's disease [3, 4], therefore MAO-B inhibiton is one of the strategies for treatment of Parkinson's disease [3, 4] as a covalent bond between the inhibitor and MAO-B is formed upon inhibiton, i.e. in clinical use are for now irreversible inhibitors of MAO-B.



Structures of reactants, transition state and products for selegiline reacting with flavin.

Geometries were optimized at the HF/6–31G(d) level of theory.



Structures of reactants, transition state and products for rasagiline reacting with flavin.

Geometries were optimized at the HF/6–31G(d,p) level.

Despite huge efforts, there is no consensus about the mechanism of catalytic step. There have been three distinct mechanism proposed, by which MAO oxidazes substrates: 1) hydride mechanism, 2) radical mechanism [5] and 3) polar nucleophyllic mechanism [6-11]. They have in common the fact that the rate-limiting step is abstraction of the α-C proton proximal to amino group at the substrate, and being picked up by the N5 atom of flavin. As up to now no mechanistic or computational studies were performed for clinically used irreversible acetylenic inhibitors selegiline and rasagiline, we did the first computational study for the reaction between flavin moiety of flavin adenine dinucleotide (FAD) co-factor and acetylenic inhibitors selegiline and rasagiline. As the nature of covalent bond, despite many studies [12], is thus far unknown, we assumed a mechanism where an adduct between acetylenic inhibitor and FAD is formed, and we got a covalently formed inhibitor-flavin adduct. We believe that polar nucleophylic mechanism adopted in our study is more probable than the radical one, as the Hammet correlation coeficient indicates the negative charge buildup upon formation of the transition state [12].The results of this quantum-chemical study are promising and together with additional experimental and theoretical work they will lead toward better understanding of the nature of MAO inhibition and design of novel inhibitors.

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Flexibility Controls Specificity of Snake Venom Metalloproteases

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Protein-Protein interfaces have crucial functions in many biological processes[1]. The large interaction areas of such interfaces show complex interaction motifs. Even more challenging is the understanding of (multi-)specificity in protein-protein binding. Many proteins can bind several partners to mediate their function[2].

A perfect paradigm to study such multi-specific protein-protein interfaces are snake venom metalloproteases (SVMPs)[3]. Inherently, they bind to a variety of basement membrane proteins of capillaries, hydrolyze them, and induce profuse bleeding. However, despite having a high sequence homology, some SVMPs show a strong hemorrhagic activity, while others are (almost) inactive[4].

Our results indicate that the activity to induce hemorrhage, and thus the capability to bind the potential reaction partners, is related to the backbone flexibility in a certain surface region[4]. A subtle interplay between flexibility and rigidity of two loops seems to be the prerequisite for the proteins to carry out their damaging function. Presumably, a significant alteration in the backbone dynamics makes the difference between SVMPs that induce hemorrhage and the inactive ones.

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Ligand Binding Study of Carbonic Anhydrase 2

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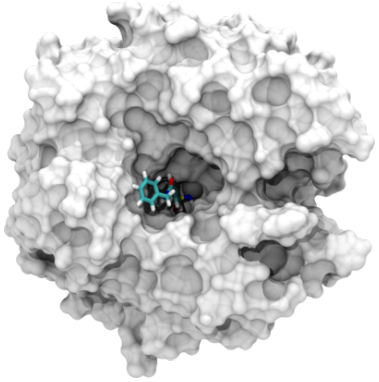
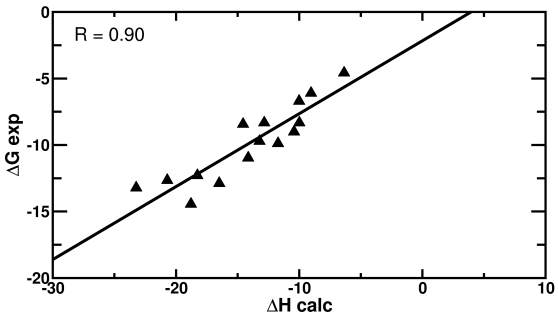
Carbonic anhydrases (CAs) are ubiquitous metalloenzymes that catalyze the reversible hydration of carbon dioxide with remarkable efficiency. CA isoforms are involved in various pathological processes including infections, tumorigenicity, osteoporosis, epilepsy, etc. and CAs have thus been the focus of many biophysical studies of protein-ligand interactions. Today, at least 25 clinically used drugs are known to display pronounced CA inhibitory properties [1].

To design a protein with particular properties, understanding the influence of residues is crucial. In this work we report on a computational strategy that allows predicting strong inhibitors and potentially beneficial mutations of the protein.

The active site of most CAs contains a $Zn(His)_3$ which is essential for catalysis. The carbonic anhydrase protein is ideal for the design of potent and selective inhibitors. Among these, arylsulfonamides, which bind tightly to the Zn ion at physiological pH (down to sub-nM), occupy a place of choice [2].





We report a Molecular Mechanics Generalized Born Solvent Approximation (MMGBSA [3]) study comparing the binding free energy for this important class of inhibitors. 18 of these sulfonamides were investigated. Using this method, not only the total binding free energy, but also the influence of a particular residue can be examined. Thus the effect of mutations on key residues on the binding can be determined.

To validate the simulations, we compare the results with published biophysical data as well as with a simulation using QM/MM simulations with the Self-consistent charge Density-Functional Tight-Binding (SCCDFTB [4]) method. Results show a high (up to $R = 0.90$) correlation between the predicted values and biophysical data.

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Impact of Tetramerization on Neuraminidase Dynamics and Binding Site Conformations

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Influenza neuraminidase (NA) is a tetrameric surface protein of the influenza virus and the target for antiviral drugs e.g. oseltamivir and zanamivir. The conformational diversity of the 150-loop was revealed by crystal structures of the group 1 neuraminidases [1] and investigated by molecular dynamics (MD) simulations [2, 3]. The open state conformation shows an additional subpocket (150-cavity) exploitable for drug design [4, 5].

We present a systematic analysis of three neuraminidases (avian 2005, pandemic 1918, pandemic 2009) with all-atom, explicit solvent MD simulations applying the Amber forcefield ff99SB [6]. Comparative simulations of monomeric, dimeric and tetrameric systems reveal that the sampled conformational phase space for the tetramer is distinctable from the monomer simulations. These findings point to a stabilization of the active conformations by the protein-protein-interface. In contrast to Amaro et al. [2, 3], we show, that backbone dynamics of the flexible 150-loop and the 430-loop are limited by interaction with adjacent neuraminidase subunits.

These results underline the importance of protein-protein-interactions in the neuraminidase tetramer for the examination of molecular flexibility. In consequence, considering these interactions is crucial for drug development and elucidating the mechanism of drug resistance.

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Probing small-molecule binding to sulfotransferases: an in silico protocol to predict metabolism and inhibition

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Sulfotransferases (SULTs) are enzymes able to metabolize diverse exogenous and endogenous molecules inside the human body. They catalyze the transfer of sulphate groups responsible for some ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties of drug candidates. Indeed, sulfonation can cause the decrease of the biological activity of drugs (e.g. increasing drug elimination) or in some cases induce toxic effects through the formation of highly reactive intermediates. Thus, the prediction of small molecule binding to SULTs can be useful for *in silico* prediction of such ADMET properties of compounds of therapeutic interest. To this end, we used molecular docking to explore the binding of known ligands within SULTs. We assessed several docking programs in order to correctly reproduce the experimental binding modes of known ligands. Further, previous studies suggest that most of these proteins are extremely challenging in part because of the presence of a large and flexible ligand-binding cavities able to interact with very diverse ligands. Employing molecular dynamics simulations and protein-ligand docking we developed an approach intending to discriminate the binders from non-binders among a large chemical compound library with the goal of predicting molecules potentially transformed by SULTs. Our results show that the developed approach may be useful for prioritizing compounds among a large compound collection.

Dynamical View of Energy Coupling Mechanisms in Active Membrane Transporters

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Membrane transporters constitute the principal players in active exchange of materials across the cellular membrane in an energy-dependent manner. These complex proteins constitute highly sophisticated, fine-tuned molecular pumps that efficiently couple various sources of energy in the cell to vectorial transport of a wide range of molecules across the membrane, often against the electrochemical gradient. Substrate binding and translocation along the transport pathway in membrane transporters are closely coupled to numerous stepwise protein conformational changes of varying magnitude and nature that are induced by and/or coordinated with the energy-providing mechanisms. A detailed description of the mechanism of membrane transporters, therefore, relies on high-resolution methodologies that can describe the dynamics of the process at an atomic level. In this talk, latest results of molecular dynamics simulations performed on a number of atomic structures of membrane transporters and the molecular events involved in their function revealed by these simulations will be presented.

Side Chain Oxidation Modulates Phenylalanine Hydroxylase Activity

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The monooxygenase phenylalanine hydroxylase (PheH, EC number 1.14.16.1) catalyzes the oxidation of L-phenylalanine to L-tyrosine at a non-heme iron active site. Molecular oxygen and the reductive co-factor tetrahydrobiopterin participate in the catalyzed redox reaction. Dysfunction of PheH prevents the commited step of phenylalanine degradation, leading to an accumulation of phenylalanine and in consequence to mental retardation, a well-studied genetic disease named phenylketonuria.

Recent studies highlight immune activation and inflammation to increase the ratio of phenylalanine to tyrosine in blood suggesting a downregulation of PheH [1]. As immune activation of macrophages is paralleled by the release of toxic reactive oxygen species, oxidative stress is discussed as chemical background for PheH dysfunction [2]. Furthermore, *in vitro* experiments showed disulfide reagents to modulate PheH activity [3].

Inspection of available X-ray structures revealed one apparent oxidizable site at two cysteine residues (Cys203, Cys334) distant from the active site. Mutations of both cysteine residues were shown to cause mild forms of phenylketonuria though their distance to the catalytic center [4,5]. Comparative molecular dynamics simulations were performed to analyze conformational differences of native PheH and the hypothetical protein oxidized at cysteine residues 203 and 334.

Starting from an X-ray structure of human PheH (PDB code 1J8U [6]) 100 ns of molecular dynamics simulations were carried out for each of the systems using the AMBER forcefield ff99SB [7]. Analyses of trajectories reveal, that cysteine oxidation modulates local dynamics in a loop region near the active site, which is experimentally known to show high flexibility and alterations of conformational behavior upon phenylalanine binding [8]. Increased flexibility of this region in the oxidized state is paralleled by a motion of the loop towards the active site reducing accessibility of the catalytic center providing a potential structural background for the oxidation-related inactivation of PheH.

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Effects of point mutation on BVDV RdRp: An In-silico study

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Bovine viral diarrhea virus (BVDV) represents a major viral pathogen in cattle and other ruminants, responsible for heavy agronomic losses every year as well as a wide assortment of diseases manifestation including resorption, mummification and abortion of dead fetus. Recently our group has reported the most potent inhibitor of the BVDV RdRp, a benzimidazole class of compound, as well as the point mutation I261M in this protein, which confers resistance to BVDV RdRp against benzimidazole compounds. Here, we investigated the effect of the I261M mutation by using a non conventional approach that includes molecular dynamics, cluster analysis, flexible docking and metadynamics. We found that the mutation affects the structure and the dynamics of the protein, particularly in the region of binding of inhibitor and this results the two different binding sites in wild and mutated proteins. Moreover, while inhibitor closes the entrance for the template in the the wild protein, in presence of the mutation a channel leading to the catalytic site are available as the inhibitor moved away from its original position during dynamics. Our results furnishes a molecular explanation of the resistance mechanism that is in good agreement with experimental data.

Effects of an amyloid-inhibiting D-peptide on the structural propensities of the Alzheimer's peptide

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Abstract:

Abnormal protein folding and aggregation are causative mechanisms underlying many different disease conditions. In the case of Alzheimer's disease abnormal aggregation of the 39 to 42-residue long amyloid beta peptides (Aβ) into neurotoxic oligomeric units has been identified as a major cause of the disease. Thus aggregation inhibitors hold a promising prospect to provide a new therapeutic approach for the management of Alzheimer's disease. A 12-residue D-enantiomeric peptide, the so-called D3 peptide, was recently demonstrated to possess inhibitory activity against Aβ1-42 oligomerisation in in vitro and in vivo experiments. In the current study we employed global optimisation and molecular dynamics approaches for gaining atomistic insight into the mode of interaction of D3 with the Aβ1-42 peptide. It was found that negatively charged residues in the N-terminal half of Aβ1-42 are the most important for mediating the demonstrated strong binding with electrostatic attraction being the principal driving force. Effects on the secondary structure of the Aβ1-42 peptide include a reduction in β-sheet and helical contents. In the second phase of the study we examined the interaction of D3 with a pentameric β-sheet assembly of the amyloid peptide employing global optimisation and Brownian dynamics methods, followed by atomic-detail conformational search using MD simulations. Insight from these studies provide us with important information about the principal driving forces of the interaction between Aβ1-42 and D3, and will help us in designing better anti-amyloid structural scaffolds.

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Hydration in discrete water – mean field, cellular automata based solvent model for calculating hydration free energies.

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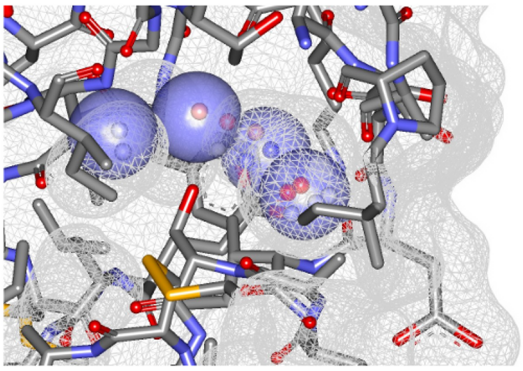
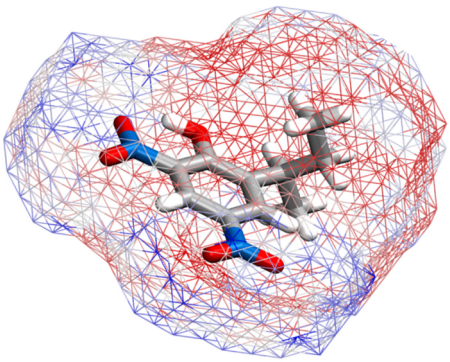
Fast and accurate predictions of hydration free energies are a long standing goal of theoretical biophysics. Despite many years of development, the existing implicit solvent models are still only moderately successful in this area. Here, a solvation model [1] based on a discrete grid of solvent cells will be presented. It utilizes a cellular automata based method to determine the solvent distribution around the solute, and mean field approach to predict the associated hydration free energy. It is computationally efficient and applicable to all compounds described by standard atomistic forcefields, including small drug-like molecules and large biomolecules such as proteins.

In our model, most solvent properties are simplified to the extreme, but those particularly important for molecular hydration: orientation dependent water hydrogen bonding and water-solute electrostatic interactions are explicitly included in the effective Hamiltonian of a solvent cell. The model does not depend on any arbitrary definition of the solute-solvent interface or microscopic surface tension. Instead, nonpolar contributions to the hydration free energies are obtained based on the calculated solvent distribution and solute-solvent dispersion. Apart from providing satisfactory predictions of hydration free energies the model is also able to reproduce some nontrivial aspects of protein hydration like dry hydrophobic cavities or isolated structural water molecules.





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Enabling medium- to high-throughput free energy calculations with the AMBER suite

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During the last decades great effort has been undertaken to develop methodologies for the computational prediction of binding affinities of potential drug molecules. In particular, three methods show promise for correctly ranking ligands by their binding affinities: molecular mechanics / Poisson-Boltzmann surface area (MM-PBSA), molecular mechanics / generalized Born surface area (MM-GBSA), and thermodynamic integration (TI) [1, 2]. Until recently, however, the analysis of large ligand data sets was hampered by the computational burden of these methods. Consequently, no setup and analyses procedures are available at present in the AMBER suite of programs [3] that allow medium- to high-throughput analyses with these methods. Instead, performing the calculations requires many manual interventions.

To enable an easy, fast, and consistent determination of binding free energies for series of related ligands binding to one target with AMBER, we developed the workflow programs WAMM (Workflow Analysis for MM-PBSA & MM-GBSA) and TIW (Thermodynamic Integration Workflow) for automated setup and analysis of MM-PBSA, MM-GBSA, and TI calculations. Based on a command file, in which the system specific parameters are defined, the programs carry out all steps required for preparation of the calculations, thus integrating tasks that had to be performed separately so far with different modules of the AMBER suite. We paid particular attention to the adaptability of WAMM and TIW to different cluster architectures and batch systems by using a template-based setup procedure, in which the required input and batch files are generated according to single template files provided by the user.

The workflow programs were successfully tested on Factor Xa inhibitors [4] with modeled complex geometries. 19 out of 25 ligands were correctly ranked in an all-pairwise manner in more than 50% of the cases. With respect to efficiency, the setup allows to compute binding free energies for tens of ligands within a week on a state-of-the-art compute cluster.

With increasing compute power and improved simulation technology in the next years, we expect that computed binding free energies for large ligand data sets will be more frequently applied for guiding lead optimization efforts. The workflow tools presented here will considerably facilitate these computations.

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