Welcome to the Molecular Modelling Workshop 2009 and Model(l)ing'09 in Erlangen!

MGMS-DS e.V.
Computer-Chemie-Centrum
Nägelsbachstr. 25, 91052 Erlangen
Germany

Sunday, September 6th - Friday, September 11th 2009

The Molecular Modelling Workshop was formerly known as the Darmstädter Molecular Modelling Workshop. The first 16 Workshops took place in Darmstadt and were hosted by Jürgen Brickmann's group. This is the 23rd Workshop in the series and the seventh to take place in its second home, Erlangen. This year, the Workshop is being held on Sunday and Monday, September 6th and 7th as a satellite meeting for Model(l)ing'09. The Molecular Modelling Workshop is the German equivalent of the Young Modellers' Forum that has a long tradition in the United Kingdom and has recently been established in Australia. These meetings are organized by the Molecular Graphics and Modelling Society in order to allow young researchers (especially graduate students) to present their work to an audience of active researchers.

Model(l)ing'09 follows Model(l)ing'97 and Model(l)ing 2001 as the third of the Annual International meetings of the Molecular Graphics and Modelling Society that has taken place in Erlangen. The Claus-Wilhelm von der Lieth Memorial Medal will be presented for the first time at this meeting. "Willi" von der Lieth was an active member, committee member and treasurer of the MGMS-DS for many years. His untimely death robbed the Society of a valued and popular member, an excellent Molecular Modeler and a good friend to many.

One reason to hold the Annual International Meeting of the MGMS in Erlangen this year is to celebrate Tim Clark's 60th birthday – albeit a little belatedly. We are grateful to the many speakers from all over the world who have agreed to come to Erlangen to ensure that this meeting will be of the very highest quality.

We wish you a pleasant and memorable stay in our city and region. We will do our very best to make you welcome and to ensure that your memories of Erlangen are positive. We are only able to do this because of the generous support of our many sponsors, who have supported us generously despite the economic crisis. Without them, meetings of this kind would hardly be possible.

So, a big thank you

- to you for coming
- to our sponsors, to the Department of Chemistry and Pharmacy, the Excellence Cluster Engineering of Advanced Materials and the Friedrich-Alexander-Universität Erlangen-Nürnberg
- to all who have made this meeting possible and especially
  - Harald Lanig – organization
  - Christof Jäger and Sebastian Schenker – Conference booklet, posters and graphics
  - Matthias Hennemann – technical support
  - Nico van Eikema Hommes – finances

Molecular Modelling Workshop 2009

Once again, we in CCC are happy to welcome you to the 23rd Molecular Modelling Workshop. The goals of the Workshop are to give graduate students and young postdocs an opportunity to present their work, to provide a forum for molecular modeling and to give young researchers the opportunity to meet established researchers, both industrial and academic. The Molecular Graphics and Modelling Society – Deutschsprachige Sektion (MGMS-DS) is, as always the organizer of the Workshop and provides financial support to enable students to attend the meeting.

We especially thank our sponsors, who have not only this year enabled us to provide an excellent program at a very low price, but many of whom have supported the Molecular Modelling Workshop consistently and generously over its entire history.

The official language of the Workshop is English.

Contributions from all branches of modeling, from life-sciences to materials modeling, are welcome.

Our invited speaker this year is

Dr. Peter Ertl
Novartis Institutes for BioMedical Research
Basel, Switzerland

Coordination of scientific program

Dr. Thomas Mietzner

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Molecular Modelling Workshop 2009

Conference Details

Location

This years Modelling Workshop and the main conference Model(l)ing'09 will take place in the building of the Institute for Organic Chemistry (OC), Henkestraße 42, 91054 Erlangen.

The lectures of the workshop will take place in the large lecture hall ("großer Hörsaal"), located on the first floor of the Organic Chemistry building, as will the plenary lectures of Model(l)ing'09 and one of the two parallel sessions. The other parallel session will take place in the small lecture hall located on the ground level of the building.

Conference Desk

The conference desk will be situated in the Institute for Organic Chemistry in the Foyer of the large lecture hall from Sunday, September 6th to Friday, September 11th during the lectures. There will be a pin board for messages close to the conference desk.

Registration

The main registration for both events takes place at the Institute for Organic Chemistry from 12:00 to 14:00 on Sunday, September 6th and from 19:00 to 22:00 on Monday, September 7th during the welcome mixer. Registration is also possible at the conference desk thereafter.

Badges

Please wear your badge at all times during the conference. Local organizers and helpers will be identifiable by badges with red background color. Please feel free to ask them for any help you may need.

Lunch

Lunch is available in many restaurants in Erlangen. A list of restaurants and a city map will be provided upon registration.

Poster Sessions

The Poster Session of the Molecular Modelling Workshop 2009 will take place from 19:00 to 20:30 on the evening of Sunday, September 6th, followed by the Workshop Buffet.

Conference Details

The Poster Sessions of Model(l)ing'09 will take place on Tuesday, September 9th and Wednesday, September 10th from 17:30 to 19:30. Please put your posters up before the session and do not forget to remove them at the end of the session.

Authors will find their posters and slot numbers in the lists provided in this booklet. The abstracts of all posters are available on the conference web site and on a CD provided upon registration.

Complementary beer and soft drinks will be available during all poster sessions. Please also take the time to visit our commercial exhibitors.

Conference Excursion

The conference excursion on Thursday, September 10th will start at 15:00 at the main Erlangen railway station and we will take the train to Nürnberg (about 25 minutes) leaving at 15:14. At the station in Nürnberg we will be met by English-speaking guides who will accompany us in groups of about 25 people through the historic old town. The tour (about 3 hours) will include the old town itself, the three main churches (Lorenzkirche, Sebalduskirche and Frauenkirche) and will end at the imperial castle where the conference dinner will take place. Please remember that the tour is by foot and for much of the time outdoors.

The excursion costs 25 EUR including the return train journey and some tickets will be available at registration for those who have not ordered them in advance.

Conference Dinner

The conference dinner will take place after the excursion in the famous Kaisersaal at the imperial castle Nürnberg.
The Nuremberg Castle is one of the most important imperial palaces dating from the Middle Ages: from 1050 to 1571 all the emperors of the Holy Roman Empire stayed in it at various times during their reign.Friedrich Barbarossa and his successors developed the existing Salian Royal Castle originating from the mid-11th century into an impressive imperial seat, as reflected in particular by the double chapel, which has been preserved in its entirety.

We have the opportunity to visit the double chapel in small groups during the dinner!

Conference Details

Bierkeller Evening

The map below shows the way to the Entla's-Keller (an den Kellern 5-7), where we have reserved tables for an informal evening on Wednesday, September 9th.

"An den Kellern" is the traditional street full of sandstone beer cellars on the Burgberg, a hill on the outskirts of Erlangen. This is the site of the traditional Bergkirchweih, Erlangen's beer festival, which takes place for 12 days at Whitsun every year and attracts about 800,000 people. The easiest way to walk to the Entla's-Keller is to take the Hauptstraße (the pedestrian precinct) past Hugenottenplatz and Schloßplatz, out of the end of the pedestrian precinct at the junction with Heuwegstraße, on to Martin-Luther-Platz, where the street runs downhill and becomes Bayreuther Straße. Continue on Bayreuther Straße until you reach the bridge over the River Schwabach. Turn right into Essenbacher Straße and then immediately left into Bergstraße, which is a small street that climbs the hill to An den Kellern. At the T-junction at the end of Bergstraße turn left and you will see the Entla's-Keller after about 100 m on the right hand side.

Awards

Molecular Modelling Workshop 2009

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

Winner: Travel bursary to the Young Modellers' Forum in the United Kingdom (travel expenses are reimbursed up to EUR 500)
2nd Winner: EUR 200 travel expenses reimbursement
3rd Winner: EUR 100 travel expenses reimbursement

Only undergraduate and graduate research students qualify for the Poster and Lecture Awards.

Model(l)ing'09

A total of three poster prizes of EUR 100 each will be awarded. The winners will be announced at the end of the meeting.

Travel Bursaries

The following delegates have been awarded an MGMS bursary to support travel to the Erlangen meeting:

Azam, Syed Sikander
University of Innsbruck, Austria

Fulle, Simone
Heinrich-Heine-Universität Düsseldorf, Germany

Krüger, Dennis
Heinrich-Heine-Universität Düsseldorf, Germany

Metz, Alexander
Heinrich-Heine-Universität Düsseldorf, Germany

Naômé, Aymeric
University of Namur, Belgium

Pal, Tuhin Kumar
Indian Institute of Technology, Kanpur, India

We thank the MGMS and the the International Society of Quantum Biology (ISQBP) for financial suppoort.

Program: Sunday, September 6th 2009

12:00-13:50	Molecular Modelling Workshop Registration
13:50-14:00	Welcome remarks / Agenda review
14:00-14:25	**Caroline Becker** *Saarland University, Saarbrücken, Germany* Design of Protein Interaction Surfaces: Prediction of Mutational Effects on Protein-Protein Binding.
14:25-14:50	**Alexander Metz** *University of Düsseldorf, Germany* From structures to hot-spots to inhibitors. Knowledge-driven design of peptidomimetic modulators of a protein-protein interaction.
14:50-15:15	**Gudrun Spitzer** *University of Insbruck, Austria* Minor Groove of DNA as Target for Drug Design.
15:15-15:40	**Sebastian Schenker** *University of Erlangen-Nürnberg, Germany* The guanidine-thiourea catalyzed nitro-Michael reaction: An ab initio study
15:40-16:00	Coffee break
16:00-16:25	**Jana Selent** *Universitat Pompeu Fabra, Barcelona, Spain* Molecular Simulation of Sodium Ions at their Allosteric Binding Sites in the Dopaminergic D2 Receptor.
16:25-16:50	**Simone Fulle** *University of Düsseldorf, Germany* Shedding light into the ribosomal exit tunnel via flexibility analysis and molecular dynamics simulation.
16:50-17:15	**Michael Kreim** *Technische Universität Darmstadt, Germany* Equilibration time of transmembrane potentials in ion channel simulations.

Program: Sunday, September 6th 2009

17:15-17:40 **Mima Staikova**
University of Toronto, Canada
Utilizing Computational Chemistry Methods as Educational Tools for Undergraduate Chemistry Courses.

17:40-18:05 **Björn Sommer**
University of Bielefeld, Germany
CELLmicrocosmos 2.1 Workshop: Applications in simplified Modeling of three-dimensional PDB Membranes.

19:00-22:00 **Poster Presentations / Buffet**
Institute for Organic Chemistry, Henkestaße 42

Program: Monday, September 7th 2009

9:00-9:25	**Robert Günther** *University of Leipzig, Germany* Comparing Apples and Oranges - How Reliable Are Molecular Docking Tools?
9:25-09:50	**Elodie Laine** *Institut Pasteur, Paris, France* Structural mobility of the anthrax toxin and search for inhibitors.
09:50-10:15	**Michael Hutter** *Saarland University, Saarbrücken, Germany* Bioisosteric Similarity of Drugs in Virtual Screening.
10:15-10:40	**Thomas Steinbrecher** *University of Freiburg, Germany* Towards the Application of Free Energy Calculations in Ligand Protein Binding Studies.
10:40-11:00	Coffee break
11:00-11:25	**Kerstin Hoehfeld** *Boehringer Ingelheim, Biberach, Germany* A Systematic Search for Scaffold Hops in PubChem.
11:25-12:15	**Invited Lecture: Peter Ertl** *Novartis Institutes for BioMedical Research, Basel, Switzerland* Estimation of synthetic accessibility score of drug-like molecules.
12:15-14:00	Lunch break
14:00-14:25	**Daniele Narzi** *Saarland University, Saarbrücken, Germany* Evidence for Proton Shuffling in a Thioredoxin-Like Protein during Catalysis.
14:25-14:50	**Jochen Heil** *Technische Universität Darmstadt, Germany* Prediciton of aqueous acidities and tautomer ratios by embedded cluster integral equation theory.
14:50-15:15	**Arun Kumar Subramanian** *University of Reading, UK* Unique Water Entering Path into Secretary Phospholipase A2 Active Site.

Program: Monday, September 7th 2009

15:15-15:40 **Tuhin Kumar Pal**
Indian Institute of Technology, Kanpur, India
In silico Mutations of Self-contacting Asp in a Protein DD-transpeptidase: Effects Probed by Molecular Dynamics Simulations.

15:40-16:00 Coffee break

16:00-16:25 **Hakan Kayi**
University of Erlangen-Nürnberg, Germany
Parameterization of AM1*

16:25-16:50 **Jörg Grunenberg**
Technische Universität Braunschweig, Germany
Selectivity in Carbohydrate Recognition: The Role of the Anomeric Effect

16:50-17:00 Poster & Lecture awards

17:00-18:00 Annual MGMS-DS General Meeting

19:00-22:00 Model(l)ing'09 Registration and Mixer / Exposition

Program: Tuesday, September 8th 2009

09:00-10:00 **Frank Neese**
University of Bonn, Germany
Catalysis with Iron – How does nature do it?

10:00-10:30 Coffee break

	DRUG DESIGN 1	METHODS QUANTUM
10:30-11:00	**Curt Breneman** *Rensselaer Polytechnic Institute Troy, NY*	**Tomasz Wesolowski** *University of Geneva, Switzerland*
11:00-11:30	**Robert Klein** *Bayer CropScience AG, Frankfurt a. M., Germany*	**Andreas Görling** *University of Erlangen-Nürnberg, Germany*
11:30-12:00	**Thierry Langer** *University of Innsbruck, Austria*	**Marek Sierka** *Humboldt Universität Berlin, Germany*
12:00-12:30	**Frank Böckler** *LMU München, Germany*	**Robert Berger** *Frankfurt Institute for Anvanced Studies, Germany*

12:30-14:00 Lunch time

14:00-15:00 **Richard Catlow**
University College London, UK
Computer Modelling of Microporous and Oxide Catalysts

15:00-15:30 Coffee break

	DRUG DESIGN 2	METHODS - CLASSICAL
15:30-16:00	**Peter Gmeiner** *University of Erlangen-Nürnberg*	**Jonathan Essex** *University Southampton, UK*
16:00-16:30	**David Ritchie** *LORIA, Nancy, France*	**Robert Deeth** *University of Warwick, UK*
16:30-17:00	**Christian Kramer** *University of Erlangen-Nürnberg, Germany*	**Matthias Ullmann** *University of Bayreuth, Germany*
17:00-17:30	**Alex Tropsha** *University of North Carolina at Chapel Hill*	**Yves Muller** *University of Erlangen-Nürnberg, Germany*

17:30-19:30 **Poster Session 1**

Program: Wednesday, September 9th 2009

09:00-10:00 **Leo Radom**
University of Sydney, Australia
Transition-Metal-Free Hydrogenation and Hydrogenolysis: A Computational Approach.

10:00-10:30 Coffee break

	DRUG DESIGN 3	MATERIALS
10:30-11:00	**Mike Hann** *GlaxoSmithKline, Stevenage, UK*	**Paul Cox** *University of Portsmouth, UK*
11:00-11:30	**Dave Winkler** *CSIRO Molecular and Health Technologies, Clayton South, Australia*	**Dirk Zahn** *Max Planck Institute for Chemical Physics of Solids, Dresden, Germany*
11:30-12:00	**Gisbert Schneider** *University of Frankfurt/Main, Germany*	**Christof Jäger** *University of Erlangen-Nürnberg, Germany*
12:00-12:30	**Trevor Howe** *Johnson & Johnson, Beerse, Belgium*	**Klaus Mecke** *University of Erlangen-Nürnberg, Germany*

12:30-14:00 Lunch time

14:00-15:00 **Arieh Warshel**
University of Southern California, CA
Multiscale Modeling of Biological Functions

15:00-15:30 Coffee break

	BIOPOLYMERS 1	PERSPECTIVES
15:30-16:00	**Harald Lanig** *University of Erlangen-Nürnberg, Germany*	**Andrew Torda** *University of Hamburg, Germany*
16:00-16:30	**Thomas Exner** *University of Konstanz, Germany*	**Marcus Meuwly** *University of Basel, Switzerland*
16:30-17:00	**Johan Åqvist** *Uppsala University, Uppsala, Sweden*	**Holger Gohlke** *University of Düsseldorf, Germany*
17:00-17:30	**Rainer Böckmann** *Saarland University, Saarbrücken, Germany*	**Dirk Guldi** *University of Erlangen-Nürnberg, Germany*

17:30-19:30 **Poster Session 2**

20:00 **Entla's Keller (Erlangen Biergarten)**

Program: Thursday, September 10th 2009

09:00-10:00 **Pavel Jungwirth**
Academy of Sciences of the Czech Republic, Prague
Ions at Aqueous Interfaces: From Water Surface to Hydrated Proteins.

10:00-10:30 **Frank Blaney "**Historic Reflections"
KA Research, Edmonton, London,UK

10:30-11:00 Coffee break

	BIOPOLYMERS 2	REACTION MECHANISMS 1
11:00-11:30	**Frank Blaney** *KA Research, Edmonton, London,UK*	**Tatyana Shubina** *University of Erlangen-Nürnberg, Germany*
11:30-12:00	**Heinrich Sticht** *University of Erlangen-Nürnberg, Germany*	**Per Siegbahn** *Stockholm University, Sweden*
12:00-12:30	**Jiří Šponer** *Academy of Sciences of the Czech Republic, Prague*	**Martin Kaupp** *University of Würzburg, Germany*
12:30-13:00	**Charlie Laughton** *University of Nottingham, UK*	**Michael Bühl** *University of St Andrews, UK*

13:00-14:30 Lunch time

14:30-19:00 **Excursion (Nürnberg)**

19:00 **Conference Dinner (Imperial Castle Nürnberg)**

Program: Friday, September 11th 2009

09:00-10:00 **Andreas Hirsch**
University of Erlangen-Nürnberg, Germany
tba

10:00-10:30 Coffee break

	FUNCTION OF PROTEINS	REACTION MECHANISMS 2
10:30-11:00	**Kennie Merz** *University of Florida, Gainesville, FL*	**Tore Brink** *Royal Institute ofTechnology (KTH), Stockholm, Sweden*
11:00-11:30	**Andreas Göller** *Bayer Schering Pharma AG, Wuppertal, Germany*	**Rainer Koch** *University of Oldenburg, Germany*
11:30-12:00	**Nigel Richards** *University of Florida, Gainesville, FL*	**Peter Politzer** *University of New Orleans, LA*
12:00-12:30	**Wolfgang Brandt** *Leibniz Institute of Plant Biochemistry, Halle(Saale), Germany*	**Henrik Zipse** *LMU Munich, Germany*

12:30-14:00 Lunch time

14:00-15:00 **Claus-Wilhelm von der Lieth Medal (MGMS-DS)**

15:00-15:20 **Poster prizes and closing remarks**

Molecular Modelling Workshop 2009 Posters

P01	**Syed Sikander Azam**	Structural and Dynamical Properties of Germanium(II) in Water: an Unusual Hydration Structure Revealed by a Quantum Mechanical Charge Field Molecular Dynamics Study
P02	**Caroline M. Becker**	Improving the Binding Affinity of the TEM1-BLIP Complex Using Computational Mutation Scannings
P03	**Frank Beierlein**	A DFT-QM/MM-Approach to Consider Polarization in Protein-Ligand Binding Free Energy Calculations
P04	**Rainer A. Böckmann**	Free energy study of ion permeation through gramicidin
P05	**Fabian Bös**	Multi-Parameter Scoring Functions for Ligand- and Structure-Based De Novo Design
P06	**Claudia Caudai**	3D Molecular Animation and Scientific Representation with Blender
P07	**Pia Dirauf**	Viral Envelope Fusion Proteins: Exploring Conformational Change with Computational Methods
P08	**Simon M. Eckard**	Saturating Dangling Bonds with GHO – Recent Developments
P09	**Federico Filomia**	Computational insight into DFG-in/out transition mechanism in MAPKs p38α.
P10	**Juliane Fischer**	Modelling of a short-chain dehydrogenase/reductase and in silico screening for potential ligands
P11	**Susanne von Grafenstein**	Structure Based Modeling on Liver X Receptors
P12	**Robert Günther**	Docking Reliability (Dr) – A Simple Measure to Compare Different Docking Approaches
P13	**Jochen Heil**	Prediciton of aqueous acidities and tautomer ratios by embedded cluster integral equation theory
P14	**Leonhard Matthias Henkes**	Modeling of the influenza A virus protein PB1-F2
P15	**Matthias Hennemann**	CypFit: A Cavity-Based Approach for the Prediction of Sites of P450-Mediated Metabolism
P16	**Thomas Herberg**	Conformational Analysis of Peptoids

Molecular Modelling Workshop 2009 Posters

P17	**Peter-Paul Heym**	Protein modelling of Arabidopsis thaliana L. PARP-1 and pharmacophore design
P18	**Anselm H. C. Horn**	Aβ42 Oligomers Emerging from Fibrils: Elucidating Effectors in Alzheimer's Disease
P19	**Christian Jäger**	Application of Structure and Ligand based Methods for the Investigation of the Flexibility of Loop Regions within a Cyclin Dependent Kinase (CDK) and the Prediction of a possible Binding Mode of Highly Selective Inhibitors
P20	**Christophe Jardin**	Specific Recognition of STAT Factors by Dual-Specificity Phosphatases
P21	**Kristin Kaßler**	Elucidation of Oligomerization Differences in Pathogenic Alzheimer's Aβ42-Amyloid Variants
P22	**Alrun N. Koller**	Temperature Jump Simulation of a ß-Hairpin by Molecular Dynamics Simulations
P23	**Hannes Kopitz**	Neither small nor unimportant, yet overlooked: How much unbound ligands contribute to the thermodynamic inhibition profile of thrombin inhibitors
P24	**Stanislav Kozmon**	Search for the Potencial Glycosyltransferase Inhibitors – Docking Study
P25	**Kristian Errebo Krantz**	Controlling the hydrolysis rate of secretory phospholipase A2 by designing phospholipid analogs: an MD and QM/MM study
P26	**Michael Kreim**	Equilibration time of transmembrane potentials in ion channel simulations
P27	**Zdeněk Kříž**	Investigating effect of ionic strength on conformational behavior of beta amyloids
P28	**Dennis M. Krüger**	Elastic potential grids: Accurate and efficient representation of intermolecular interactions for fully-flexible docking
P29	**Klaus R. Liedl**	Shape Based Screening and Thermodynamic Characterization of Minor Groove Binding Ligands
P30	**Jesper J. Madsen**	Enzymatic hydrolysis of cellulose fibers: A computational study

Molecular Modelling Workshop 2009 Posters

P31	**Daniele Narzi**	Evidence for Proton Shuffling in a Thioredoxin-Like Protein during Catalysis
P32	**Gül Altınbaş Özpınar**	Semi-empirical and DFT Study on Urea Clusters
P33	**Christopher Pfleger**	Improved consistency of protein flexibility analyses by fluctuating hydrogen bond networks
P34	**Felix Rausch**	Detailed investigation of the catalytic mechanism of monoterpene synthases by combined quantum and molecular mechanical calculations
P35	**Eva Schulze**	Modeling of a monoterpene synthase and analysis of product distribution
P36	**Riad Schulz**	Selectivity of New Fluorogenic Caspase 8 Tetrapeptide Substrates can be Rationalized with Automated Docking Analysis
P37	**Farag Selim**	Homology modelling of the human adenosine A2B receptor based on X-ray structures of bovine rhodopsin, the β2-adrenergic receptor and the human adenosine A2A receptor
P38	**Björn Sommer**	CELLmicrocosmos 2.1: A Software Approach for the Modeling of three-dimensional PDB Membranes
P39	**Peter R. Tentscher**	Aqueous solvation of small anions: polarization of the solvent due to electron transfer
P40	**Panesso Ingrid Liliana Vargas**	Rescuing the p53 Function by Disrupting the MDMX-p53 Interaction via In Silico Screening of Potent Antagonists
P41	**Simon Michael Vogel**	Towards a Reproducible Generation of Test Sets for the Evaluation of in silico Screening Methods by Immediate Neighborhood Classification
P42	**Rainer Wilcken**	Halogen bonding as valuable interaction in drug design – Investigation of interaction types by Quantum Chemical calculations
P43	**Jürgen Wittmann**	Rational Design of Enzyme Promiscuity by Molecular Model(l)ing: Theoretical Concepts towards non-Natural Biocatalytic Reactions
P44	**Marcel Youmbi Foka**	Solvation Models based on the Multipole Electrostatic Approach with Minimal Valence spd-basis sets

Molecular Modelling Workshop 2009 Posters

P45	**Marco Matthies**	RNA Sequence Design, Newtonian Dynamics and Mean Fields

Model(l)ing'09 Posters (Session 1)

P01	**Caroline M. Becker**	Design of Protein Interaction Surfaces: Prediction of Mutational Effects on Protein-Protein Binding
P02	**Rainer A. Böckmann**	Free energy study of ion permeation through gramicidin
P03	**Claudia Caudai**	3D Molecular Animation and Scientific Representation with Blender
P04	**Pia Dirauf**	Viral Envelope Fusion Proteins: Exploring Conformational Change with Computational Methods
P05	**Guillermina Estiu**	Computer Aided Molecular Design Studies of HDAC Inhibitors
P06	**Federico Filomia**	Computational insight into DFG-in/out transition mechanism in MAPKs p38α.
P07	**Georgios Fradelos**	The cooperative effect of the hydrogen-bonded chains in the environment of a $\pi \rightarrow \pi^*$ chromophore
P08	**Robert Günther**	Docking Reliability (Dr) – A Simple Measure to Compare Different Docking Approaches
P09	**Matthias Hennemann**	CypFit: A Cavity-Based Approach for the Prediction of Sites of P450-Mediated Metabolism
P10	**Thomas Herberg**	Conformational Analysis of Peptoids
P11	**Anselm H. C. Horn**	Aβ42 Oligomers Emerging from Fibrils: Elucidating Effectors in Alzheimer's Disease
P12	**Christophe Jardin**	Specific Recognition of STAT Factors by Dual-Specificity Phosphatases
P13	**Antreas Kalli**	Investigation of Talin Interactions with Lipid Bilayers using Coarse-Grained Molecular Dynamic Simulations
P14	**Thomas W. Keal**	QM/MM excited state optimisation with DL-FIND and ChemShell
P15	**Alexander Klenner**	Self-organizing binding pose generation for adaptive ligand-receptor docking
P16	**Kristian Errebo Krantz**	Controlling the hydrolysis rate of secretory phospholipase A2 by designing phospholipid analogs: an MD and QM/MM study

Model(l)ing'09 Posters (Session 1)

P17	**Zdeněk Kříž**	Investigating effect of ionic strength on conformational behavior of beta amyloids
P18	**Alexandre S. Lawrenson**	Quantitative-Structure Activity Relationships for a Series of Aminoquinoline Compounds Against Chloroquine Sensitive and Resistant Strains of the Malaria Parasite
P19	**Miguel Machuqueiro**	The role of the biological membrane on kyotorphin's conformational space.
P20	**Adrian Malik**	Design of telomere targeting agents
P21	**Aymeric Naômé**	Molecular dynamics simulation of 8-oxoguanine containing DNA fragment reveals altered hydration and ion binding patterns
P22	**Chanisorn Ngaojampa**	Development and validation of a new mesoscopic model for double helical DNA
P23	**Gül Altınbaş Özpınar**	Theoretical Investigation on Vilsmeier-Haack Complex Formation
P24	**Horacio Pérez-Sánchez**	High throughput in-silico screening against flexible protein receptors
P25	**Felix Rausch**	Detailed investigation of the catalytic mechanism of monoterpene synthases by combined quantum and molecular mechanical calculations
P26	**Jeffrey R. Reimers**	Quantum consciousness is shown not to be biologically feasible by modelling Fröhlich condensates, by modelling entanglement at the MP2 and CASPT2 levels, and by consideration of microtubule dynamics
P27	**Tobias Schmidt**	In Vitro-Driven Virtual Screening for Dengue Virus Methyltransferase Inhibitors
P28	**Eva Schulze**	Modeling of a monoterpene synthase and analysis of product distribution
P29	**Farag Selim**	Homology modelling of the human adenosine A2B receptor based on X-ray structures of bovine rhodopsin, the β2-adrenergic receptor and the human adenosine A2A receptor
P30	**Björn Sommer**	CELLmicrocosmos 2.1: A Software Approach for the Modeling of three-dimensional PDB Membranes

Model(l)ing'09 Posters (Session 1)

P31	**Arun K. Subramanian**	Molecular Docking Studies to Gain Insights into Binding Interactions of Novel DACA Analogs - G-Quadruplex DNA.
P32	**Tim ten Brink**	Systematic Studies on the Influence of Ligand Protonation in ProteinLigandDocking
P33	**Andrew E. Torda**	RNA Sequence Design, Newtonian Dynamics and Mean Fields
P34	**Paolo Tosco**	Open3DQSAR: a new open-source pharmacophore explorer based on chemometric analysis of molecular interaction fields
P35	**Urszula Uciechowska**	Prediction of ligand binding free energies of novel thiobarbiturates to the human NAD+ dependent histon deacetylase Sirt2
P36	**Simon M. Vogel**	To Kill the Immortal: Systematic Evaluation and Application of a Virtual Screening Protocol for Inhibitors of the X-linked inhibitors of Apoptosis
P37	**Rainer Wilcken**	Targeting the Y220C mutant of the tumor suppressor protein p53: Virtual screening and biophysical testing towards new scaffolds for protein stabilization

Model(l)ing'09 Posters (Session 2)

P01	**Frank Beierlein**	A DFT-QM/MM-Approach to Consider Polarization in Protein-Ligand Binding Free Energy Calculations
P02	**Fabian Bös**	Virtual Screening for R-Groups Including Prediction of Activity Contributions
P03	**Paulo J. Costa**	Molecular Dynamics Studies on Triply Interlocked Capsule: Structural and Diffusion Studies
P04	**Simon M. Eckard**	Saturating Dangling Bonds with GHO – Recent Developments
P05	**Vítor Félix**	Using GAFF in Phospholipid Membrane Simulations: the effect of a calix[4]arene derivative in a DOPC bilayer
P06	**Juliane Fischer**	Modelling of a short-chain dehydrogenase/reductase and in silico screening for potential ligands
P07	**Tim Geppert**	ProBinder: Protein-Protein Docking
P08	**Paul Hawkins**	Conformer generation: Identifying and learning from failures
P09	**Stefan Henrich**	Virtual screening for covalently bound compounds to disrupt protein dimerization of thymidylate synthase
P10	**Peter-Paul Heym**	Protein modelling of Arabidopsis thaliana L. PARP-1 and pharmacophore design
P11	**Michael C. Hutter**	Bioisosteric Similarity of Molecules Based on Structural Alignment and Observed Chemical Replacements in Drugs
P12	**Adrián Kalászi**	Flexible 3D alignment and its application in virtual screening
P13	**Kristin Kaßler**	Elucidation of Oligomerization Differences in Pathogenic Alzheimer's Aβ42-Amyloid Variants
P14	**Robert Klein**	New relationships between bond order and bond length
P15	**Stanislav Kozmon**	Search for the Potencial Glycosyltransferase Inhibitors – Docking Study
P16	**Michael Kranz**	Expect the Unexpected – Ligand Binding Modes in Pde4
P17	**Elodie Laine**	Structural mobility of the anthrax toxin and search for inhibitors
P18	**Martin Lepšík**	Molecular dynamics-QM/MM Quenching as a Tool for Structure-based Drug Design: Increasing the Potency of Inorganic Polyhedral Metallacarboranes as Novel HIV Protease Inhibitors

Model(l)ing'09 Posters (Session 2)

P19	**Jesper J. Madsen**	Enzymatic hydrolysis of cellulose fibers: A computational study
P20	**Jane S. Murray**	The Expanded σ-Hole Concept
P21	**Daniele Narzi**	Evidence for Proton Shuffling in a Thioredoxin-Like Protein during Catalysis
P22	**Cristian Obiol-Pardo**	Multiscale modeling of drug-induced arrhythmia: the hERG potassium channel level
P23	**Tuhin Kumar Pal**	Understanding Carbonyl-Carbonyl Self-contacts in High Resolution Protein Crystal Structures: Quantum Mechanical Calculations and Molecular Dynamics Study
P24	**Ralph Puchta**	Water exchange processes on solvated zinc cations. $[Zn(H_2O)_4L]_2+\cdot 2H_2O$ with L = sp, sp2, sp3 nitrogen donor ligands
P25	**Sascha Rehm**	Increasing the temperature optimum of Pseudomonas fragi lipase - A molecular dynamics study
P26	**Julie Roy**	Application of Multiple Microsecond Molecular Dynamics Simulations and Quartz Crystal Micxrobalance Experiments to the Study of Ligand Recognition by the Major Urinary Protein.
P27	**Riad Schulz**	Selectivity of New Fluorogenic Caspase 8 Tetrapeptide Substrates can be Rationalized with Automated Docking Analysis
P28	**Jana Selent**	Molecular Simulation of Sodium Ions at their Allosteric Binding Sites in the Dopaminergic D2 Receptor
P29	**Raman Sharma**	A Novel Drug for Uncomplicated Malaria: Chemoinformatics Methods for Compound Selection in a High Throughput Screening Program
P30	**Thomas Steinbrecher**	Direct simulation of electron transfer reactions in DNA radical cations
P31	**Mahesh Sundararajan**	Revisiting EPR pr oper ties of Nitr ic oxide bound Myoglobin with High Field EPR spectr oscopy and QM/MM calculations
P32	**Peter R. Tentscher**	Aqueous solvation of small anions: polarization of the solvent due to electron transfer

Model(l)ing'09 Posters (Session 2)

P33	**Frank Tristram**	Implementation of Backbone Flexibility on In-Silico Drug Discovery
P34	**Panesso I. L. Vargas**	Virtual Screening for novel inhibitors of the pVHL-HIF1α-interaction as a therapeutic approach in ischemic diseases
P35	**Tim Werner**	Identification of preferred binding pockets in the Histamine H4 Receptor using pseudoreceptor-based pocket selection and Molecular Dynamics Simulation

Lectures

Molecular Modelling Workshop 2009

September 6th - 7th 2009

Design of Protein Interaction Surfaces: Prediction of Mutational Effects on Protein-Protein Binding

Caroline M. Becker[1], Alexander Benedix[1], Bert L. de Groot[2], Amedeo Caflisch[3], and Rainer A. Böckmann[1*]

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Proteins are involved in most processes in the cell and therefore an important target in pharmaceutical research. The activity of processes can be influenced by modifying the stability or the binding behavior of the involved proteins by mutation. For an efficient identification of possible mutation-sites a fast calculation of the free energy of proteins is crucial.
Here we developed and implemented a fast and reliable method (CC/PBSA) [1] for the prediction of the change in stability of proteins and binding affinity of protein-protein complexes upon mutation. The energy function of CC/PBSA is based on gas phase energies, solvation free energies and entropic contributions. The protein flexibility is taken into account by generating random conformations based on geometrical constraints only applying the CONCOORD[2] program. CC/PBSA was developed and validated on a test set of more than 900 mutants of various proteins and protein-protein complexes, including non-alanine, non-conservative and multiple mutations.
We applied CC/PBSA on the TEM1-BLIP complex, which is important in bacterial antibiotic resistance. The results of single- and double-point alanine scanning are used to detect hot spots, cooperative effects, and the corresponding energy distribution. These binding propensities allow us to suggest complexes with increased binding affinity and stability.
CC/PBSA is freely accessible on our **web-server**:
http://ccpbsa.bioinformatik.uni-saarland.de

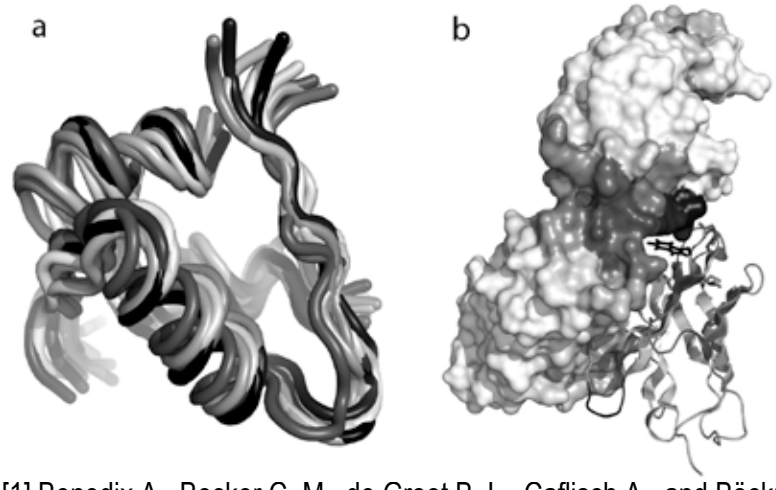

Figure 1. (a) Flexibility included in CC/PBSA by generating a realistic conformational ensemble using CONCOORD[2]. (b) Color-coded change in flexibility upon B_TRP52ALA mutation in an antigen-antibody complex (1vfb). Regions with increased flexibility are colored dark.

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From structures to hot-spots to inhibitors. Knowledge-driven design of peptidomimetic modulators of a protein-protein interaction.

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Becker, Y., Frankfurt am Main/D, Wichmann, C., Frankfurt am Main/D,
Koch, J., Frankfurt am Main/D, Grez, M., Frankfurt am Main/D

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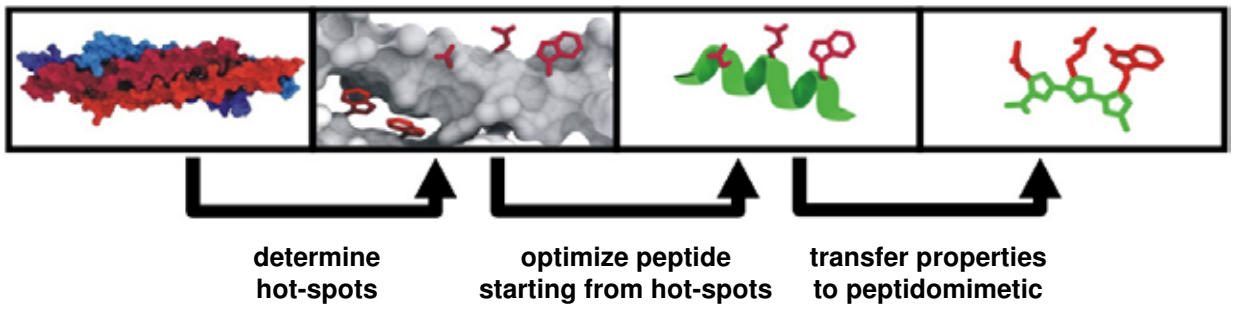
Homotetramerization of the α-helical NHR2 domain of the AML1/ETO fusion protein is an essential prerequisite for the onset of acute myeloid leukaemia (AML) in 12 % of all cases. Inhibiting this tetramerization from NHR2 dimers efficiently prevents carcinogenesis. [1, 2] Here, we combine computational and experimental methods with the aim to design a small molecule binding to the tetramerization interface in order to inhibit NHR2 tetramerization.

For a rational design of peptidic and peptidomimetic inhibitors of NHR2 tetramerization, we first determine the hot-spots of binding by a MM-GB/SA binding free energy decomposition. [3] In the second step, we use the hot-spot information to identify a peptidic lead, which is further optimized by a peptide array affinity assay. [4] The optimization cycle is assisted by a sequence-sensitive physicochemical QSAR (quantitative structure activity relationship) model based on data from the affinity assay. In the last step, drug-like modulators will be designed by decorating an α-helix mimetic teroxazole scaffold [5] with analogs of essential side chains identified in previous steps.



Following this strategy, we were already able to successfully identify hot-spot residues in the NHR2 tetramerization interface and confirm them in a cell-based assay and mouse model. Likewise, a 18mer containing these hot-spots was found to inhibit NHR2 tetramerization, albeit at millimolar concentrations.

Literature:

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Minor Groove of DNA as Target for Drug Design

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Small minor groove binding molecules have been found to influence DNA-dependent processes. Their affinity is high enough to prevent transcription factors from interaction with the DNA. Some of the minor groove binders can be even designed to target only specific DNA sequences. Thereby, they are able to influence transcription, which provides the possibility to systematically regulate the synthesis of proteins. Unfortunately, all highly sequence-selective minor groove binders have the same structural scaffold, which includes a number of amide bonds, and therefore lack metabolic stability. We adopted methods originating from chemoinformatics to merge experimental data with our knowledge on the dynamics of the biomolecular interface of DNA. We demonstrated that we are able to reproduce sequence specificity by a pharmacophore modeling approach [1] and built a comprehensive database containing all known minor groove interactions within complexes of DNA with different ligands [2]. An analysis of the database revealed that the known minor groove binding scaffolds are far from optimally fitting the hydrogen bonding patterns presented by DNA [3]. Therefore, screened compound databases for new ligands. We validated the ligands by isothermal titration calorimetry to understand the thermodynamics of ligand binding [4].

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The guanidine-thiourea catalyzed nitro-Michael reaction: An ab initio study

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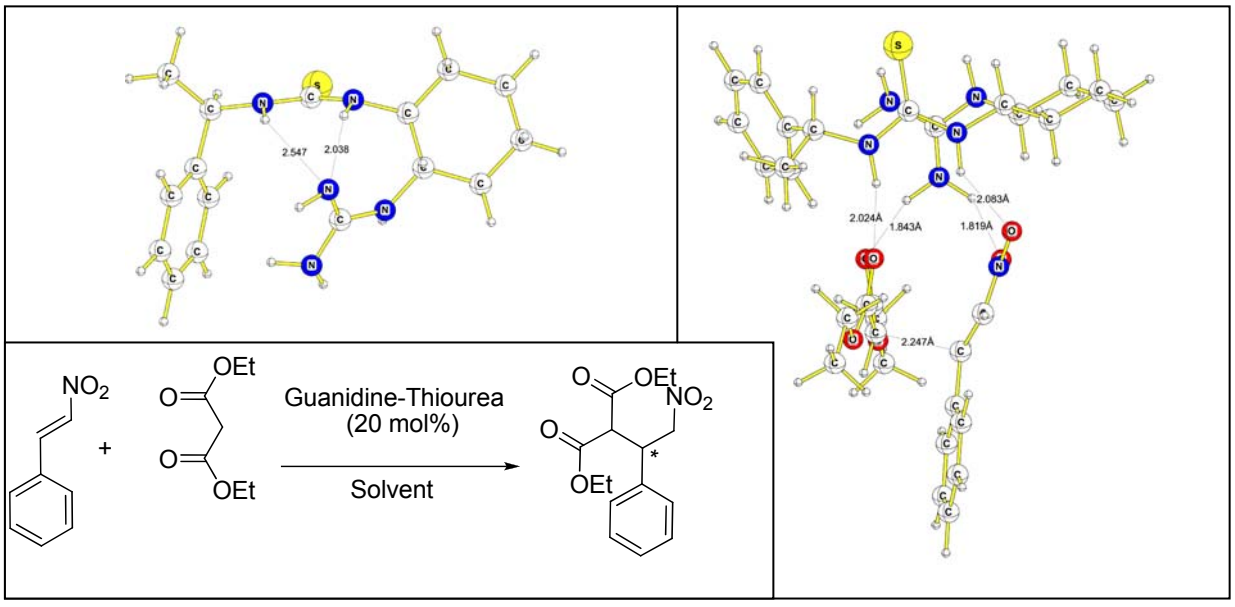
Brønstedt-basic, Lewis-acidic bifunctional catalysts are gaining importance in organocatalysis. The possibility of tuning the properties of bifunctional catalysts by modifying the spatial orientation of the two active functional groups is highly attractive for organic chemists. A large number of successive approaches have been reported up to date [1].

Recently, our group and that of Jacobsen reported the first successful application of primary amine-thiourea organocatalysts with the synchronous dual activation of a nucleophile and an electrophile in nitro-Michael addition reactions [2]. Based on this catalyst, a new type of chiral guanidine-thiourea catalyst has been developed in our laboratory. In comparison to literature known thiourea-amine catalysts, the catalyst shows superior activity, but only low enantioselectivity. An extensive DFT study was carried out to rationalize the experimental findings. The study is based on a Model by Hamza et al.[3] for amine thiourea catalysts which had to be extended due to the higher complexity and flexibility of our system. With the computational data we are able to describe the effect of the unique H-bond patterns formed by these types of catalysts and employ them to reproduce the experimental findings. Based on the computational data, we propose an improved catalyst that will be investigated in out laboratories.



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MOLECULAR SIMULATION OF SODIUM IONS AT THEIR ALLOSTERIC BINDING SITES IN THE DOPAMINERGIC D_2 RECEPTOR

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Sodium ions have been shown to play an important role in the modulation of agonist and antagonist binding to the well-known D3.32 of various G-protein coupled receptors (GPCRs)[1]. The putative sodium binding site is assumed to be in the center of a pyramidal hydrogen-bonding network formed by the residues D2.50, S3.39, N7.45, and S7.46[2]. In an effort to understand the mechanism of the sodium-induced effect on receptor function, we investigated computationally the mobility of sodium ions in the sodium-sensitive D_2 receptor embedded in a membrane bilayer environment under physiological ionic strength conditions. Using long-term unconstrained molecular dynamics simulations for a total of 10 μs, we studied for the first time the pathway of a sodium ion entering the GPCR from the extracellular site along negatively charged residues into the receptor and its electrostatic interaction in the pyramidal hydrogen-bonding network at D2.50. The simulation reveals on one hand the energetics which drives sodium ion's mobility. On the other hand, the study discloses diverse sodium ion binding sites in between D3.32 and D2.50 which we propose as being part of the sodium-induced effect on ligand binding in the D_2 receptor.

Our finding supports the existence of a sodium ion trapped in the pyramidal hydrogen-bonding network and provides novel implication of a sodium ion as an allosteric modulator for sodium-sensitive GPCRs, an issue highly relevant in drug design.

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Shedding light into the ribosomal exit tunnel via flexibility analysis and molecular dynamics simulation

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The ribosome is a large ribonucleoprotein complex that carries out protein synthesis in all kingdoms of life by translating genetic information encoded in mRNA into the amino acid sequence of a protein. The nascent polypeptides escape the peptidyl transferase center through the ribosomal exit tunnel that spans the entire large subunit. The tunnel is involved in the control of co-translational protein folding processes, the regulation of elongation and inhibition of the protein synthesis by antibiotics [1,2]. Most of the present knowledge about the function of the ribosomal exit tunnel is derived from X-ray crystallography. This only provides us with static snapshots along conformational transitions, whereas the underlying dynamical processes remain largely unclear. E.g., there is still some disagreement over whether the ribosomal tunnel dynamically promotes the passage of the nascent peptide chain or whether the peptides pass passively through the tunnel.

First, I present global and local flexibility characteristics of the ribosomal exit tunnel revealed by constraint counting on new topological network representations of large ribosomal subunits from four different organisms [3,4]. The analyses provide critical insights into the role of the ribosomal exit tunnel during protein synthesis. The flexibility characteristics of the tunnel will be used to answer questions such as: Does the ribosomal tunnel dynamically promote the passage of the nascent peptide chain or does it act as a passive tube? To what degree can proteins fold in the tunnel? What is the origin of species-selectivity of antibiotics binding?

The above flexibility analysis says nothing about the direction and amplitude of existing motions and thus, questions related to the collective dynamics within the tunnel remain unresolved. To bridge this gap, I will present results from an all atom MD simulation of the large ribosomal subunit in explicit solvent.

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Equilibration time of transmembrane potentials in ion channel simulations

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The transmembrane potential in double lipid bilayer simulations arises physically from charge imbalances between cations and anions [1]. Although one would expect rapid equilibration of the ion distribution in a pure electrolyte solution, this is not the case if the ion density fluctuations are coupled to the slow protein/membrane dynamics near the interface. Therefore, very long equilibration times can be expected for properties such as the transmembrane potential that is given by inverting Poisson's equation using the average charge density as input.

Here we extend the blocking analysis for computing the statistical inefficiency [2, 3] in order to derive a rigorous error estimate for equilibrium observables that are important for analyzing simulations of ion channels in a solvated membrane environment. The inefficiency allows for an estimation of the correlation time connected with fluctuating properties and serves as a correction in order to calculate reliable error bars from variances. By treating the statistical inefficiency as a dynamic variable, we show that equilibration times for electrolyte solutions exposed to a protein/membrane interface are much longer than suggested by bare analysis of typical protein descriptors, such as backbone root mean square deviations. Results are presented for the Kcv channel [4, 5] embedded in a lipid membrane in KCl solution, subjected to both single as well as double bilayer geometry. For the latter, equilibration times and error estimates for the transmembrane potential under various conditions are discussed.

Please note that the content of the talk is also presented as a poster.

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Utilizing Computational Chemistry Methods as Educational Tools for Undergraduate Chemistry Courses

Mima Staikova

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Student exposure to computational methods as part of the undergraduate curriculum became a reality in the Chemistry Department, University of Toronto, during the last few years. Recently, one 300-level course, and three 400-level courses included "hands-on" quality quantum mechanical computational methods based on the Gaussian computational suite of programs which proved to be extremely beneficial to the learning process.

Expanding further the involvement of theoretical methods to additional senior level courses through new approaches for computer modeling, particularly in the fields of bioorganic and bioinorganic chemistry will enrich the undergraduate learning, and make the graduates more competitive on the job market in the areas of biotechnology, pharmaceutical drug development, and materials science.

Several examples will be presented to illustrate the involvement of molecular modeling applications in the Chemistry curriculum.

CELLmicrocosmos 2.1 Workshop: Applications in simplified Modeling of three-dimensional PDB Membranes

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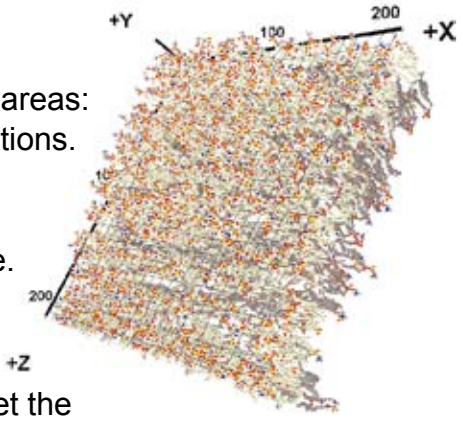
Background: Only a few programs support membrane computation and/or modeling. They enable the user to create very simple structured membrane layers and usually assume a high level of knowledge. Much work need to be invested, before the sophisticated work dealing with algorithms can begin. The CELLmicrocosmos 2 project develops a tool providing a user-optimized, modular and scalable concept for the computation of membrane (bi-)layers: The MembraneEditor (CmME).

Results: To accelerate the membrane generation process, the computation is geometry-based, supporting fast to more complex membrane generations. CmME is based on the integration of two different types of PDB [1] models: Lipid models, provided for example by the HIC-UP database [2], are integrated with editable percental distribution values and algorithms. Proteins are inserted and aligned manually into the bilayer by a user interface. The resulting membrane is exported in PDB format. Compatibility with other programs is provided by extensive export settings. High lipid densities are possible through advanced packing algorithms. A Plugin-Interface supports the development of applied distribution algorithms.

Conclusions: CmME has been extended and tested to meet the requirements of different PDB visualization programs as well as molecular dynamics (MD) simulation environments like Gromacs [3]. The documentation and a Java Webstart version, requiring only an internet connection and Java 6, are accessible at:

http://Cm2.CELLmicrocosmos.org



Workshop: The workshop will focus at different application areas:
- How to model and visualize different Membrane Compositions.
- How to choose the appropriate algorithm.
- How to generate MD compatible membranes.
- How to develop own algorithms using the Plugin-Interface.

Outlook: The support of multilayers, an automatization process for protein placement and access to the atomic level for the membrane algorithms will be integrated to meet the advanced requirements of the simulation community. In the near future, exported membranes additionally could be integrated into virtual cell environments.

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Comparing Apples and Oranges – How Reliable are Molecular Docking Tools?

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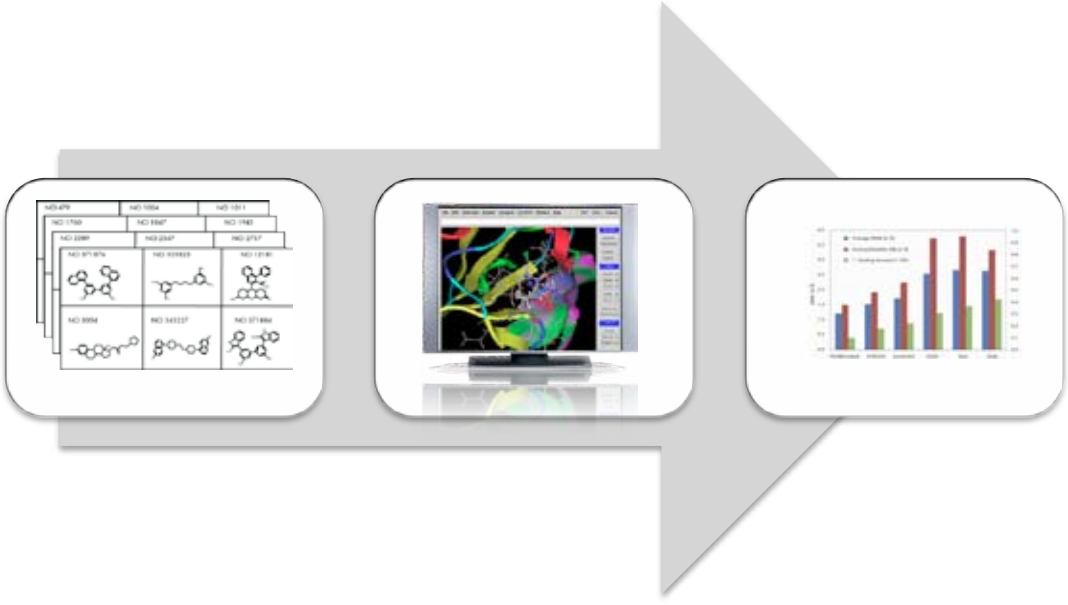
The development a novel drug is a time consuming and expensive process. Besides the identification of the target, a significant amount of time and money is required to screen large libraries of compounds for drug candidates. Computational methods, namely molecular docking techniques, play, thus, an important role in the drug discovery process. Employing these techniques, scientists hope to identify novel drug candidates by screening chemical libraries *in silico*.



A number of different molecular docking approaches have emerged in the last two decades. As all of these methods employ different algorithms and methods to create and evaluate the proposed protein-ligand complexes, a direct comparison is difficult. Moreover, some programs might be particularly more suited for docking on certain classes of proteins, *e.g.*, kinases or proteases.

In this presentation, we will introduce a novel measure to compare the reliability of docking methods: the Docking Reliability (DR). This measure can be regarded as a standard deviation of all predicted protein-ligand poses of a data set with respect to the experimentally determined structures. In contrast to the commonly used average rmsd value, it considers wrongly predicted poses of a data set more stringent.

Based on a highly diversified data set comprising 100 protein-ligand complexes from the Protein Data Bank, numerous well-established docking programs will be compared. The resulting DR values will help the scientist to determine that particular docking program, which delivers the most reliable results with respect to the target under investigation.

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Structural mobility of the anthrax toxin and search for inhibitors

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Among the toxins secreted by *Bacillus anthracis*, responsible for anthrax disease, the oedema factor EF is an adenylate cyclase that overproduces cAMP from ATP. The accumulation of cAMP provokes cellular dysfunction and enables EF to impair host immune defences [(1)]. EF is activated by calmodulin (CaM), involved in many calcium signalling pathways. The level of calcium bound to CaM was shown to influence the stability and even the formation of the EF-CaM complex [(1,2,3)].

The analysis of 15-ns molecular dynamics simulations of EF-CaM, CaM being loaded with zero, two or four Ca^{2+} ions, permitted to characterise CaM conformational plasticity and to propose a model for the EF-CaM interaction [(5)]. The electrostatic effect of calcium throughout the residue network of the complex was also modelled, within a framework unifying dynamical correlations and energetic influences [(6)]. Furthermore, the large conformational transition undergone by EF upon interaction with calmodulin was described. Calculations based on the Conjugate Peak Refinement algorithm [(7)] enabled to obtain plausible intermediate conformations. Such conformations were used to drive the search for inhibitors of the toxin, in an approach combining both computational and experimental methods. The *in silico* strategy, involving virtual screening of an allosteric pocket at the surface of the protein, identified several active molecules able to fully inhibit EF activity [(8)].

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Bioisosteric Similarity of Drugs in Virtual Screening

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Choosing compounds for screening is difficult problem due the vast chemical space. The question is thus which compounds are most likely to be hits. The comparison of drugs that all target the same enzyme, however, shows reoccurring chemical modification throughout all therapeutic categories. These so-called bioisosteric replacements[1] comprise simple exchanges of terminal atoms as well as more complex structural modifications, such as ring closures or rearrangements of larger fragments. To detect and evaluate all kinds of replacements we have designed an approach that adopts the algorithmic concept used to assess the homology of amino acid sequences to chemical molecules. The mutual exchange frequencies between distinct atom types are expressed in a substitution matrix.[2] Likewise, pair-wise alignment between the molecules is constructed using dynamic programming,[3] with the compounds being represented as unique SMILES. To obtain the actual exchange frequencies, we refined an initial matrix based on observed chemical replacements[4] by collecting the generated alignments of 1353 drugs from 33 therapeutic categories in an automated procedure. To compute the mutual bioisosteric similarity between two molecules a specific function has been derived that makes use of the alignment.[5]

To asses the suitability of this bioisosteric similarity for virtual screening, we compared the recovery of known drugs against the background of other substances. The majority of drugs possess a higher similarity within the same class than compared to substances from the ZINC[6] or the Prous Science Drugs of the Future database.[7] Likewise, drugs for the same target are usually recovered at higher values of similarities than compared to other methods based on most common substructure and fingerprint approaches. Moreover, nondrugs without any pharmaceutical function exhibit considerably lower similarities than actual drugs.

Furthermore, this bioisosteric similarity can be used to express the chemical diversity within a given compound class. We found that e.g. inhibitors of the HIV Reverse Transcriptase are more divers than Angiotensin-II Antagonists and Tetracycline Antibiotics.

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Towards the Application of Free Energy Calculations in Ligand Protein Binding Studies

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Abstract

Cells contain a multitude of different chemical reaction paths running simultaneously and without interference next to each other. This amazing feat is enabled by molecular recognition, the ability of biomolecules to form stable and specific complexes with each other and with their substrates. A better understanding of this process, i.e. of the kinetics, structures and thermodynamic properties of biomolecule binding, would be invaluable in the study of biological systems. In addition, as the mode of action of many pharmaceuticals is based upon their inhibition or activation of biomolecule targets, predictive models of small molecule receptor binding are very helpful tools in rational drug design. Since the goal here is normally to design a new compound with a high inhibition strength, its most important thermodynamic property is the binding free energy ΔG^0. The prediction of binding constants has always been one of the major goals in the field of computational chemistry, because the ability to reliably assess a hypothetical compound's binding properties without having to synthesize it first would save a tremendous amount of work. The different approaches to this question range from fast and simple empirical descriptor methods to elaborate simulation protocols aimed at putting the computation of free energies onto a solid foundation of statistical thermodynamics. While the later methods are still not suited for the screenings of thousands of compounds that are routinely performed in computational drug design studies, they are increasingly put to use for the detailed study of protein ligand interactions. This talk will focus on molecular mechanics forcefield based free energy calculations and their application to the study of protein ligand interactions. We will describe recent advances in methodology and some exemplary studies of molecular dynamics simulation based free energy calculations.

A Systematic Search for Scaffold Hops in PubChem

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Scaffold hopping is the bioisosteric replacement of structural elements of a molecule and plays an important role in lead optimization. The focus of this study was the replacement process in which only the central core of a compound is substituted.[1,2] There are several computational ligand-based methods that propose these scaffold replacements for a given query using different theoretical backgrounds. Surprisingly, retrospective examples to validate the output of these programs are rare.

A systematic search for scaffold replacements was developed to extend the number of known retrospective examples of scaffold hops. It was performed in datasets of active compounds of 71 selected PubChem bioassays. The method searches for molecule pairs with common but disconnected substructures because these are candidates for scaffold hopping. A set of selected scaffold hop candidates was aligned with the programs FieldAlign[3] and ParaFit[4] to explore the agreement in interaction potential of the according scaffold pairs. As both programs use a combination of electronic features and shape information for the alignment, a scaffold hop is supposed to show a high score for the alignment that conserves the orientation of the common substituents.

The search identified several scaffold replacements in the PubChem experimental data that also possess bioisosteric similarity and that therefore represent retrospective examples of successful scaffold hops.

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Estimation of synthetic accessibility score of drug-like molecules

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Ranking, or prioritization of molecules is needed in many areas of modern drug discovery process. Molecules are normally prioritized according to criteria such as drug-like properties, natural-product likeness, predicted biological activity or freedom to operate with respect to intellectual property. Since sooner or later the selected structures will be resynthesized or derivatized, prioritization also by their synthetic accessibility, should be included early on.
The method for estimation of synthetic accessibility score (SAscore) which we have developed at Novartis and is presented here is based on a combination of fragment contributions and a complexity penalty. Fragment contributions have been calculated based on the analysis of fragments in one million representative molecules from PubChem and therefore one can say that they capture historical synthetic knowledge stored in this database. The molecular complexity score takes into account the presence of non-standard structural features, such as large rings, non-standard ring fusions, stereocomplexity and molecule size. The method has been validated by comparing calculated SAscores with ease of synthesis as estimated by experienced medicinal chemists for a set of 40 molecules. The agreement between calculated and manually estimated synthetic accessibility is very good with $r^2 = 0.89$.
Various possible applications of the new synthetic accessibility score in drug discovery processes will be also discussed, including purchasing samples for screening, selecting hits from high-throughput screening for follow-up, or ranking molecules generated by various *de novo* design approaches.

See also:
P. Ertl and A. Schuffenhauer, Estimation of synthetic accessibility score of drug-like molecules based on molecular complexity and fragment contributions, *Journal of Cheminformatics*, 1:8 2009 (open access)
http://www.jcheminf.com/content/1/1/8

Evidence for Proton Shuffling in a Thioredoxin-Like Protein during Catalysis

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Proteins of the thioredoxin (Trx) superfamily catalyze disulfide-bond formation, reduction and isomerization in substrate proteins. All members of the Trx family with thioldisulfide oxidoreductase activity contain the characteristic Cys-X-X-Cys motif in their active site. Here, using Poisson-Boltzmann-based protonation-state calculations based on 100-ns Molecular Dynamics simulations, we investigated the catalytic mechanism of DsbL, the most oxidizing Trx-like protein known to date[1]. We observed several correlated transitions in the protonation states of the buried active-site cysteine and a neighboring lysine coupled to the exposure of the active-site thiolate. These results support the view of an internal proton shuffling mechanism during oxidation crucial for the uptake of two electrons from the substrate protein. Intramolecular disulfide-bond formation is probably steered by the conformational switch facilitating interaction with the active-site thiolate. A consistent catalytic mechanism for DsbL, probably conferrable to other proteins of the same class, is presented[2]. Our results suggest a functional role of hydration entropy[3] of active-site groups.

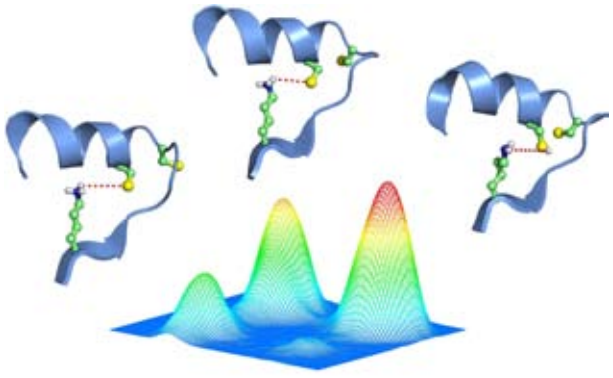

Figure 1. Switches in the active site cysteine dihedral angles of the thioredoxin-like protein DsbL are suggested to induce a protein internal proton shuffling crucial for the function of this enzyme.

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Prediciton of aqueous acidities and tautomer ratios by embedded cluster integral equation theory

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The "embedded cluster reference interaction site model" (EC-RISM) approach combines statistical-mechanical integral equation theory and quantum-chemical calculations in order to predict thermodynamic data for chemical reactions in solution [1]. The electronic structure of the solute is determined self-consistently with the structure of the solvent which is described by 3D RISM integral equation theory. The coupling is achieved by mapping the continuous solvent-site distribution onto a set of discrete background charges ("embedded cluster") and using it as an additional contribution to the molecular Hamiltonian. Recent progress in the understanding of conceptual and numerical features of the integral equation approximations [2] allows computations on hundreds of compounds in a reasonable time with good accuracy.

We report results from the application of the EC-RISM methodology to the prediction of aqueous pK_a values and of tautomer ratios for small organic molecules. We discuss critically important parameters that influence the accuracy of the approach, such as the adequate treatment of multiple conformations, the choice of the quantum-chemical level of theory, as well as the force field governing nonpolar solute-solvent interactions.

Please note that the content of the talk is also presented as a poster.

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Unique Water Entering Path into Secretary Phospholipase A_2 Active Site

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Secretory phospholipases A_2 ($sPLA_2$s) constitute a family of interfacially active mammalian enzymes that catalyze the cleavage of *sn*-2 ester bond of glycerophospholipid substrates resulting in lysophospholipid and free fatty acid [1]. $sPLA_2$-IIA has proven to be especially interesting in therapeutic intervention since elevated levels of $sPLA_2$-IIA is present in the microenvironment surrounding different types of tumors [2]. This has provided the basis of a new tumor activated drug delivery concept, which relies on the administration of $sPLA_2$ degradable liposomes, which deliver and release the therapeutics at the site of the target tumor [3]. We have previously shown that $sPLA_2$ can hydrolyze different phospholipid analogs with varying efficiency. The observed differences in activities could be explained in terms of substrate-protein interactions impairing with the catalytic reaction or steric hindrance interfering with an incoming water molecule that acts as a nucleophile in the enzymatic reaction [4]. This observation raised the question whether water molecules that act as the nucleophile enter the active site through a unique passage. To address this question, we have performed a series of molecular dynamics simulations of $sPLA_2$ complexed with natural substrate or a prodrug (chlorambucil covalently bound to phospholipid) and focused mainly on the water movement. We have included the prodrug, since it has experimentally been shown that the prodrug is more efficiently hydrolyzed by $sPLA_2$ than the natural substrate. The simulations revealed that there is no "in-built" water channel in the protein, but a previously reported hydrogen bonding network of $sPLA_2$ [5] acts as the water attraction site (referred as anchor site – Fig.1A). Once water molecules are attracted into the anchor site, they are guided by a diagonally placed aromatic residue located below it to move towards His47. Upon forming contacts with His47 N, the catalytic water molecule gets adjusted to sit in the right orientation with substrate C22 such that hydrolysis can occur. MD simulations highlighted that binding of the prodrug results in displacing an aliphatic amino acid forming the active site boundary, leading to enlargement of the anchor site cavity. Thus a 2 fold increase in the inflow of bulk waters was observed into the active site of $sPLA_2$ - drug complex (Fig.1B).

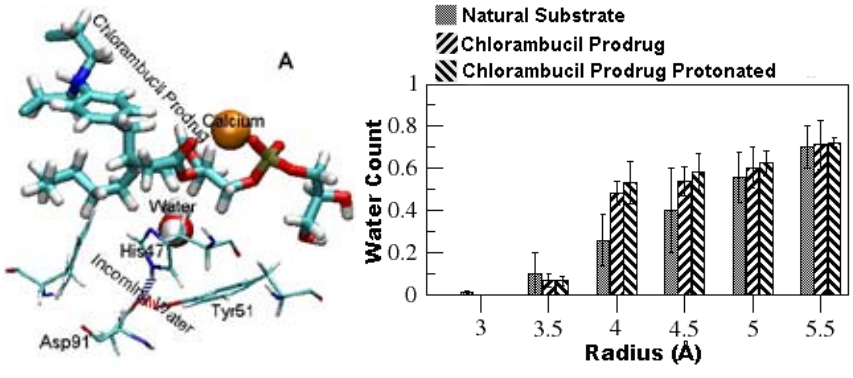

Fig.1. A. The geometry of amino acids inside the active site, B. Plots of relative water counts into the active site.

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*In silico M*utations of Self-contacting Asp in a Protein DD-transpeptidase: Effects Probed by Molecular Dynamics Simulations

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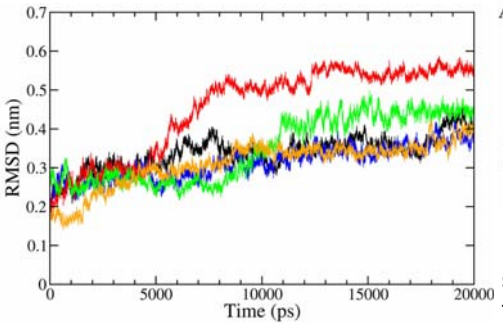
Non-covalent interactions have significant influence on the folding, structural stability and biological function of proteins. They are also known to modulate the biomolecular dynamics. Majority of non-covalent interactions occur between amino acids that are sequentially well separated. However, certain amino acids can participate in non-covalent interactions due to intra-residue contacts. For example, sidechains of Asp residues can interact with their own backbone functional groups. Our earlier studies[1] on two independent datasets of high-resolution protein crystal structures demonstrated that a significant number of Asp residues are involved in sidechain (Oxy)…mainchain (Nit) [SC(O)…MC(N)] type of self-contacts within a stringent cutoff of ≤ 2.75Å, many of them could be attributed to self-hydrogen bonds. Residue accessible surface area calculations show that when the self-contacting residues are buried they have less number of neighbouring polar contacts, indicating they might exist in a relatively more hydrophobic environment. Such self-contacts presumably occur to optimize the polar interactions with the exposed polar groups in a hydrophobic environment. To keep the sidechain at close proximity to its mainchain, they exhibit a preference for gauche$^+$ (g^+,+60°) sidechain dihedral (N–C^α–C^β–C^γ, Chi1). Thus, it could be anticipated that their role in maintaining local structural stability is of importance.

Crystal structures are snapshots and thus, represent a protein as a static molecule. But in normal physiological conditions, proteins are in constant motion. To ascertain whether self-contacts are maintained in a dynamic system and to unravel the structure-function relationship we took to *in silico* mutations followed by molecular dynamics simulation (MD). We carried out multiple MD on DD-transpeptidase[2] (PDB: 1ES5) in which the self-contacting Asp residue (D97 in wildtype protein, WT) is mutated to Ala (D97A), Thr (D97T) and Leu (D97L) based on structural studies on DD-peptidase/β-lactamase superfamily. In another incidence we even changed the sidechain dihedral from g^+ to g^- (–60°, the most preferred for Asp in general, CHI) to check the dihedral preference to maintain self-contact. Intra-residue hydrogen bond due to SC(O)...MC(N) in self-contacting D97 was restored (CHI) and was stable throughout the simulations for both CHI and WT. For D97A the structure is highly destabilized as evident from the RMSD plot (red worm in Fig.1 and D in panel figure). The structural deformation in helix-5 (blue in Fig.1) is quite distinct in D97A. Such destabilization is due to loss of self-contact which instigate disruption of helix-helix interactions and occurs almost 20Å away from the mutation site (shown in arrow). Thus "*in silico*" mutation studies reveal the importance of self-contacting residues in the structure and stability of proteins and their possible role in the function of this protein. Our investigation hold promises to give structural insight into conformational restructuring, active site modulation and drug resistance.



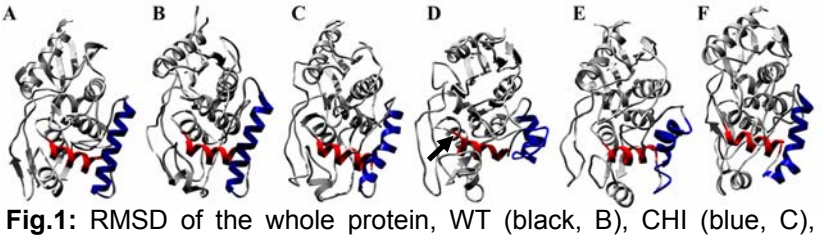


Fig.1: RMSD of the whole protein, WT (black, B), CHI (blue, C), D97A (red, D), D97T (orange, E) and D97L (green, F). The snapshots in the panel (B-F) saved at the end of 20ns of simulation time. WT and CHI are very much close to the starting structure (A).

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Parameterization of AM1*

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Our extension of the AM1 [1] semiempirical molecular orbital theory, named AM1* [2], uses the original AM1 parameters and theory unchanged for the elements H, C, N, O and F, and *d*-orbitals for the elements starting from second long row on the periodic table [2,3,4,5,6,7]. In addition to using of *s*, *p* and *d*-orbitals, new elements have been parameterized with two-center core-core parameters, rather than Gaussian functions used to modify the core-core potential in AM1. Now AM1* parameters are available for H, C, N, O and F (which use the original AM1 parameters), Al, Si, P, S, Cl, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Br, Zr, Mo (slightly modified Voityuk and Rösch's AM1(d) [8] parameters for Mo), I and Au. The performance and typical errors of AM1* are discussed and compared with available NDDO Hamiltonians.

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Selectivity in Carbohydrate Recognition: The Role of the Anomeric Effect.

Jörg Grunenberg

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Selectivity in carbohydrate recognition holds great promise in various medical applications. We have chosen the experimentally well established α/β anomer selectivity of artificial receptors as a theoretical case study in order to debunk the reason for the β anomer preference. The artificial receptor sugar complexes are promising models for a better understanding of the natural carbohydrate recognition by proteins, because their size allows for a detailed analysis on the atomistic resolution using 1) empirical force fields and 2) more rigorous quantum chemical methods. The relative energies of association have been evaluated in the gas phase and in chloroform since non-polar solvents mimic the absence of water in globular proteins with buried binding pockets. It has been observed that the α/β anomer complexes are iso-energetic, while the measured selectivity stems solely from the solvated carbohydrates mirroring just the anomeric energy differences. Further analysis of the non-covalent interactions by means of generalized compliance constants[1] (relaxed force constants) assign the anomeric effect to significant differences in intra-carbohydrate hydrogen bond strengths.

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Lectures

Model(l)ing'09

September 7th - 11th 2009

Catalysis with Iron – How does nature do it?

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High-valent iron sites play a fundamental role in bioinorganic chemistry as reaction intermediate in heme- and nonheme iron enzymes. To elucidate their geometric and electronic structure and function is therefore a key in understanding the reaction mechanisms of these enzymes. In recent years, we have – in close collaboration with our experimentally working project partners - studied a variety of mono- and dinuclear iron sites in proteins and model complexes. The lecture will stress the impact of the combination of quantum chemistry and spectroscopy for the elucidation of the structures of short lived intermediates that are not amenable to crystallographic studies.

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Modeling '09 Title and Abstract

Curt M. Breneman, Professor
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Title: "Advancing the state of the art in prospective statistical learning and data mining: A critical look at multi-task learning (MTL) methods, validation strategies and appropriate applications."

Abstract: The perceived value and acceptance of statistical learning methods within integrated drug discovery strategies has historically been uneven, but is now following a generally upward trend. This increase can be attributed to several factors, including widespread adoption of more robust learning methods, proper application of modeling results and appropriately managed expectations. This presentation will focus on four important new technologies being developed in our group that address these issues, including multi-task learning (MTL) for qHTS data extraction and biological response profiling, the Rank Order Entropy (ROE) technique for model validation and the RS-Predictor algorithm for making CYP metabolic site predictions. Each of these methodologies has a specific place within the drug discovery workflow, and provides an example for a specific type of learning method, domain of applicability, and level of expectation.

Model(l)ing 09, Erlangen, September 7-11, 2009

ABSTRACT:

Title: Docking and Scoring Protocol for Structure-based Virtual Screening

Authors: Robert Klein, G. Lange, J. Albrecht, M. Rarey, I. Reulecke, N. Schneider

Docking protocols and scoring functions for structure-based virtual screening and ligand design are aiming at identifying the preferred ligand orientations and conformations (poses) within a protein and estimating the protein-ligand binding affinities. Classical force field approaches perform quite well in pose prediction, i.e. they provide binding energies suitable to compare different conformations and poses of one ligand. However, force field energies are too inaccurate to reliably compare complexes with different ligands. Moreover, solvent effects are usually taken into account as corrections to the force field terms at the cost of significantly more computational effort and/or additional inaccuracies. We present a virtual screening protocol which uses an empirical pose generator and a classical force field for refining and filtering the poses. The poses are then scored with our novel scoring function HYDE. HYDE evaluates hydrogen bonds and solvent effects solely based upon solvent accessible surfaces, exp. logP values of small molecules and a new water theory. HYDE parameters are not fitted towards experimental protein-ligand binding energies. Nonetheless, our docking protocol provided superior hit enrichments in various validation runs.

Pharmacophore-based Activity Profiling: Efficient Guidance for Medicinal Chemists

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Targeted Rescue of the Destabilized p53 Mutant Y220C - *In silico* and Biophysical Screening in a "Novel" Binding Site

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The tumour suppressor p53 is inactivated because of mutations in some 50% of human cancers. About a third of the mutations lower the melting temperature of the protein, leading to its rapid denaturation. Small molecules that bind to those mutants and stabilize them could be effective anti-cancer drugs.[1] The mutation Y220C, which occurs in ~75,000 new cancer cases per annum, creates a surface cavity that destabilizes the protein by 4 kcal/mol, at a site that is not functional.[2] Using a structure-based *in-silico* screening approach, we were able to identify a structural scaffold binding to this "novel" binding site. The virtual high throughput-screening was complemented by biophysical screening and characterisation of the hits and was followed by rational and computational drug design.[3] PhiKan083, a leadlike structure containing the carbazole scaffold, binds to the "novel" cavity with a dissociation constant of ~150 μM. It raises the melting temperature of the mutant and slows down its rate of denaturation. We have solved the crystal structure of the protein-PhiKan083 complex at 1.5 Å resolution. The structure implicates key interactions between the protein and ligand and conformational changes that occur on binding, which provide a basis for lead optimization. We have studied structure-activity relationships of various carbazole derivatives to learn more about the binding site. Further rounds of in silico screening and design have yielded additional scaffolds with interesting new binding modes. We have found that the Y220C mutant is a "druggable" target well suited for developing and testing novel anti-cancer drugs based on protein stabilization.

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The use of the orbital-free effective embedding potential in modeling electronic excitations in condensed phase

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The orbital-free effective embedding potential is a local multiplicative potential which can be expressed as is a functional of two electron densities: that of the investigated embedded subsystem (ρ_A) and that of the environment (ρ_B) [1]. The analytic form of this functional is not known although it known for some particular analytically solvable cases [2]. In practical applications, this potential is approximated using some explicit analytical expressions for its the kinetic- and exchange-correlation components of unknown analytic form ($v_t^{nad}[\rho_A,\rho_B] = \frac{\delta T_s[\rho]}{\delta\rho}\Big|_{\rho=\rho_A+\rho_B} - \frac{\delta T_s[\rho]}{\delta\rho}\Big|_{\rho=\rho_A}$ and $(v_{xc}^{nad}[\rho_A,\rho_B] = \frac{\delta E_{xc}[\rho]}{\delta\rho}\Big|_{\rho=\rho_A+\rho_B} - \frac{\delta E_{xc}[\rho]}{\delta\rho}\Big|_{\rho=\rho_A}$, respectively):

$$v_{emb}[\rho_A,\rho_B;\vec{r}] \approx \tilde{v}_{emb}[\rho_A,\rho_B;\vec{r}] = v_{ext}^B(\vec{r}) + \int \frac{\rho_B(\vec{r}')}{|\vec{r}'-\vec{r}|}d\vec{r}' + \tilde{v}_{xc}^{nad}[\rho_A,\rho_B](\vec{r}) - \tilde{v}_t^{nad}[\rho_A,\rho_B](\vec{r})$$

where tildas denote analytic expressions approximating the exact quantity. The potential $\tilde{v}_{emb}[\rho_A,\rho_B;\vec{r}]$ can be used in the whole family of computational schemes differing in:

- The choice for the auxiliary quantities to represent the density ρ_A: either orbitals of the non-interacting reference system as introduced in our original work [1], the "wavefunction" of the multiconfigurational form [3], or the one-matrix [4]. In all the above cases, the potential $v_{emb}[\rho_A,\rho_B;\vec{r}]$ (but not necessarily its approximant $\tilde{v}_{emb}[\rho_A,\rho_B;\vec{r}]$) assures that a given computational method leads to the density $\rho_A+\rho_B$ which minimized the ground state energy of the total system under the following constraint: $\rho_{total} \geq \rho_B$.

- The way the density ρ_B is generated.

- The subsequent use of the embedded orbitals (or embedded wavefunction or embedded one-matrix) to derive observables.

In the present work, we provide examples of recent studies using the potential $\tilde{v}_{emb}[\rho_A,\rho_B;\vec{r}]$ to obtain electronic spectra of organic molecules in various environments [5, 6].

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Orbitals in Quantum Chemistry

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Orbitals, on the one hand, are often considered as auxiliary quantities without physical meaning for various reasons. Slater determinants, e.g., Hartree-Fock or Kohn-Sham determinants, are invariant with respect to unitary transformations of the occupied orbitals. Within density-functional theory (DFT) orbitals frequently are considered as quantities that merely generate the electron density but have no other meaning. In the limit of a full configuration interaction wave function orbitals just serve as one-electron basis functions. On the other hand, orbitals underly the thinking of quantum chemists. The concept of bonding or antibonding orbitals, the definition of electronic configurations, or the characterization of electronic transitions as excitations of electrons between occupied and unoccupied orbitals are examples that show the ubiquitous use of orbitals in quantum chemistry. Indeed orbitals in some sense can even be 'observed' in experiment. To demonstrate this point, examples of STM images that can be directly related to individual orbitals obtained by DFT methods are presented [1]. A crucial question is which orbitals are those corresponding to the thinking of quantum chemists or to experimental results. It is shown that one choice could be Kohn-Sham orbitals obtained by novel DFT methods which treat the local Kohn-Sham exchange potential exactly and thus are free of unphysical Coulomb self-interactions [2]. The concept of a new generation of DFT methods based on orbital-dependent functionals is presented [3].

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Recent Developments in Solid-State Quantum Chemical Methods Within the TURBOMOLE Program Package

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This talk will address recent developments in solid-state computational methods within the TURBOMOLE[1] program package. One of them is the periodic electrostatic embedded cluster method (PEECM).[2] It is an electrostatic embedding scheme which takes advantage of the periodic fast multipole method (PFMM) and is particularly designed for combined QM/MM approaches. The PFMM is based on the multipole expansion and used in the PEECM to provide the correct Madelung potential within the local quantum mechanical (QM) region due to a periodic array of point charges of any dimensionality, i.e., three-, two-, and one-dimensional periodicity. In contrast to embedding methods based on Ewald summation the PEECM approach takes only a negligible fraction of the total computational cost of a QM calculation. Even for the largest calculations presented here, which involve QM clusters with over 8000 basis functions, the total CPU time spent on the embedding part did not exceed 30 seconds on a single CPU.

In the second part of the talk, a new formulation of the resolution of identity approximation for the Coulomb term[3] will be presented, which uses atom-centered basis and auxiliary basis functions and treats molecular and periodic systems of any dimensionality on an equal footing. Converged Coulomb lattice sums are obtained using chargeless linear combinations of the atom-centered auxiliary basis functions. The Coulomb series are partitioned in near- and far-field portions which are treated through an analytical integration scheme employing two- and three-center electron repulsion integrals and the PFMM, respectively, operating exclusively in real space. Our preliminary implementation demonstrates consistent accuracy of the method across molecular and periodic systems.

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Quantum chemical methods for modelling of vibrational-electronic transitions in systems with hundreds of atoms

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Vibrational-electronic (vibronic) transitions are involved in a number of key phenomena including electron transfer, energy transfer, light absorption and photoluminescence. One of the complicating factors in the detailed modelling of these processes is the huge density of vibronic states that imposes severe constraints on the applicability of state resolved vibronic structure methods.

We have developed recently a unifying framework for the time-dependent and time-independent treatment of such processes, which combines the efficiency of time-dependent approaches in obtaining vibronic spectral profiles with the possibility to conveniently extract state resolved information [1]. Besides sum rules for rigorous prescreening of Franck-Condon and Herzberg-Teller integrals in the harmonic approximation at finite temperature [2,3], we employ also time-independent cumulant expansions that provide access to vibrational-electronic spectra at low resolution [4]. This scheme has been implemented in the vibronic structure program hotFCHT [1,5].

In this presentation, the underlying methodological framework will be outlined and its application to various types of spectroscopy will be presented.

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Computer Modelling of Microporous and Oxide Catalysts

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Computer modelling provides a range of powerful tools for exploring catalytic processes at the molecular level. In particular, modelling allows detailed characterisation of active site structures and of reaction mechanisms; and the techniques are particularly powerful when used in conjunction with experimental investigations. We will illustrate the current state-of-the-art of this field by summarising recent work in two classes of heterogeneous catalyst:

- Microporous materials, where the catalytic action is due to the presence of acid or metal sites. We will describe how the structures, properties, reactivities and formation mechanisms of such centres can be investigated in detail using a range of electronic structure techniques. We will show how, in addition to the conventional Bronsted and centre, reaction of water with zeolites can generate a fascinating range of hydrogen containing defect centres. We will also describe modelling of metal centres based on transition metal substititutionals in framework sites, with strong emphasis on microporous titanosilicate catalysts, where we will again show that reaction with water can create a range of sites which play important roles in catalytic processes.

- Metal oxide and oxide supported metal catalysts, where we will present modelling studies both of active site structures and reaction mechanisms in a range of systems including methanol synthesis catalysts.

Using Spherical Harmonic Virtual Screening Tools to Compare and Classify HIV Entry Inhibitors for the CXCR4 and CCR5 Co-Receptors

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Violeta Pérez-Nueno, Institut Químic de Sarriá, Barcelona

HIV entry inhibitors have emerged as a new generation of anti-retroviral drug that block viral fusion with the CXCR4 and CCR5 membrane co-receptors. In the last few years, many such entry inhibitors have been developed, and several are currently in clinical trials. However, because no crystal structures for the co-receptor proteins are available, the binding modes of the known inhibitors within the co-receptor extracellular pockets need to be analyzed using site-directed mutagenesis and computational experiments.

Here, we present a comparison of the performance of computational ligand-based and receptor-based virtual screening (VS) approaches to find CXCR4 and CCR5 antagonists that could potentially serve as HIV entry inhibitors [1]. In particular we describe the use of the spherical harmonic (SH) based ParaSurf and ParaFit programs [2,3] as a fast and robust way to calculate and compare the shapes of multiple small molecules [4], and we present a novel SH consensus-shape clustering technique to cluster and classify the diverse families of CCR5 antagonists in order to help understand the topology and occupation of the CCR5 exrta-cellular pocket [5].

The VS comparison was carried out using a library assembled by us consisting of 672 known CXCR4 and CCR5 inhibitors and some 4700 similar presumed inactive molecules [1]. For each receptor, the library was queried using known binders, and the enrichment factors of the resulting virtual hit lists were analyzed. Overall, ligand-based shape-matching searches yielded higher enrichments than receptor-based docking. Receiver-operator-characteristic performance analyses for both the CXCR4 and CCR5 receptors showed that the consensus shape matching technique gives better VS enrichments than the other shape-matching and docking VS techniques studied. Furthermore, the consensus-shape clustering results show that the CCR5 ligands may be grouped into four structural families which appear to bind within three main sub-sites within the extra-cellular receptor pocket.

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A Surface-Integral Model for $logP_{OW}$ and a Local Hydrophobicity

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Surface-integral models are quantitative structure-property relationships QSPRs in which a local property is integrated over the entire surface of a molecule to obtain the target property

$$P = \int_O f\left(l_1, l_2, \ldots\ldots l_n\right) d \quad \approx \sum_{i=1}^{ntri} O f\left(l_1^i, l_2^i, \ldots\ldots l_n^i\right) A^i$$

where P is the target property, $f(l_1,l_2,\ldots\ldots l_n)$ is a function of the n local properties $l_1,l_2,\ldots\ldots l_n$ and the integral runs over the molecular surface O. In practice, the integral is replaced by a numerical integration over a triangulated surface consisting of *ntri* tesserae. The local properties are obtained from an evaluation of the electronic orbitals calculated semiempirically with AM1.

We have developed a new scheme to calculate a local hydrophobicity based on binning the range of local surface properties instead of using polynomial expansions of the base terms. The basic local properties used are molecular electrostatic potential (MEP), local ionization energy (IEL), local electron affinity (EAL), local hardness (HARD), local polarizability (POL) and the local field normal to the surface (FN).

The model has been fitted to the integral of the local hydrophobicity, the distribution coefficient between octanol and water $logP_{OW}$, based on ~10.000 compounds available from literature. It has been validated on ~1.250 compounds from literature and an inhouse validation set of ~750 compounds from Boehringer-Ingelheim. The model compares similar or slightly favorable to the best models commercially available. It is independent of previously unknown substructures and enables plotting the local hydrophobicity to the molecular surface to illustrate hydrophobic hotspots and pinpoint favorable modifications.

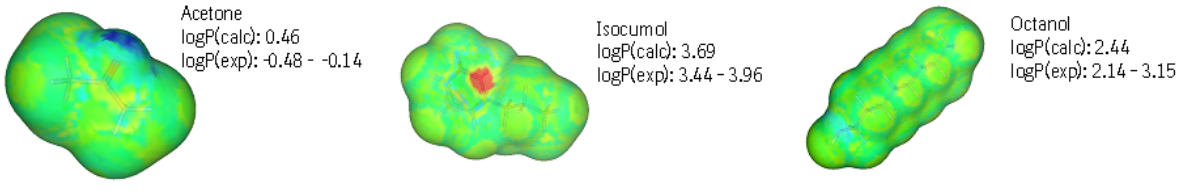

Figure 1: Hydrophobic Surfaces and $logP_{OW}$ calculated for some sample molecules

Chem(o)informatics exploration of the entire biological data continuum for building predictive chemical toxicity models

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A wealth of available biological data such as those from EPA's ToxCast Phase I (http://www.epa.gov/ncct/toxcast/) requires new computational approaches to link chemical structure, short-term bioassay results, and chronic *in vivo* toxicity responses. We advance the predictive QSAR modeling workflow that relies on effective statistical model validation routines and implements both chemical and biological (i.e., in vitro assay results) descriptors of molecules to develop *in vivo* chemical toxicity models. We have developed two distinct methodologies for in vivo toxicity prediction utilizing both chemical and biological descriptors. In the first approach, we employ biological descriptors directly in combination with chemical descriptors to build models. Obviously, this approach requires the knowledge of biological descriptors to make toxicity assessment for new compounds. Our second modeling approach employs the explicit relationship between *in vitro* and *in vivo* data as part of a two-step hierarchical modeling strategy. First, binary QSAR models using chemical descriptors only is built to partition compounds into classes defined by patterns of *in vitro – in viv*o relationships. Second, class specific conventional QSAR models are built, also using chemical descriptors only. Thus, this hierarchical strategy ultimately affords the external predictions using chemical descriptors only. We will present the results of applying both strategies to ToxCast Phase I and similar data. Our studies suggest that utilizing *in vitro* assay results as biological descriptors afford prediction accuracy that is superior to both the conventional QSAR modeling that utilizes chemical descriptors only or *in vivo* effect classifiers based on in vitro biological response only.

Multi-resolution modelling of membrane-drug permeation

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Drug permeation is critically important for determining the efficacy of a pharmaceutical compound – drugs must cross cell membranes to reach their binding sites. While the theoretical framework for calculating small molecule permeabilities through lipid bilayers is well understood, the computational cost of performing the necessary computer simulations using all-atom molecular dynamics is prohibitive for its general use. Methods of simplifying these simulations are therefore urgently needed.

Coarse-graining is one such approach. Groups of atoms are subsumed into single interaction sites, interacting through modified intermolecular potentials. In this talk, the development of a novel coarse-grain membrane model is presented, which includes shape anisotropy and a realistic treatment of electrostatics. This model is compatible with standard atomistic potentials, and it has therefore been combined with atomistic representations of small molecules to allow permeability coefficients to be calculated. The physical properties of the membrane model will be reported and discussed, along with the calibration of the coarse-grain/atomistic potential, and its use in the context of multi-resolution modelling of drug permeation.

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Computer Modelling for Transition Metal Systems: DFT Accuracy at MM Prices

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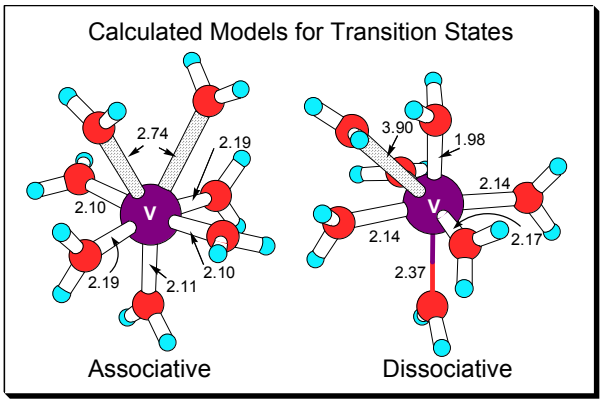
Open-shell transition metal complexes are often associated with complicated electronic structures. Consequently, theoretical coordination chemistry has tended to focus on quantum methods, e.g. density functional theory (DFT), which treat these electronic effects explicitly. However, while DFT has revolutionalised the application of quantum methods in transition metal (TM) chemistry, ALL QM approaches, including DFT, are relatively slow compared to classical simulation methods like molecular mechanics (MM). However, conventional MM is, in general, not suited to TM systems since it has a poor description of the all-important d electron effects. Our solution is to marry a simple model of d-electrons – ligand field theory – with conventional MM to generate ligand field molecular mechanics (LFMM).[1] The LFMM method captures the essential physics of metal-ligand binding and thus emulates DFT but at least three orders of magnitude faster. Moreover, the unique nature of the coordinate bond does not limit LFMM simply to modelling minimum-energy structures – we can also treat reaction mechanisms in which metal-ligand bonds are made and broken. This presentation will describe the unique features of the LFMM model and illustrate its application to coordination complexes,[2] copper metalloenzymes,[3] Jahn-Teller effects[4, 5] and water exchange at divalent metal centres.[6]



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pH-dependent pK_a Values in Proteins – A Theoretical Analysis of Protonation Energies with Practical Consequences for Enzymatic Reactions†

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Because of their central importance for understanding enzymatic mechanisms, pK_a values are of great interest in biochemical research. It is common practice to determine pK_a values of aminoacid residues in proteins from NMR or FTIR titration curves by determining the pH at which the protonation probability is 50%. The pH dependence of the free energy required to protonate this residue is then determined from the linear relationship $G_{\mathrm{prot}} = RT \ln 10\ (\mathrm{pH} - \mathrm{p}K_a)$ where R is the gas constant and T the absolute temperature. However, this approach neglects that there can be important electrostatic interactions in the proteins that can shift the protonation energy. Even if the titration curves seem to have a standard sigmoidal shape, the protonation energy of an individual site in a protein depends non-linearly on pH. To account for this non-linear dependence, we define pK_a values for individual sites in proteins that depend on pH. Two different definitions are discussed. One definition is based on a rearranged Henderson-Hasselbalch equation, the other definition is based on an equation that was used by Tanford and Roxby to approximate titration curves of proteins. In the limiting case of weak interactions, the two definitions are equivalent. We discuss how these two differently defined pK_a values are related to the free energy change required to protonate a site. Using simple examples, we demonstrate that the interactions between protonatable residues in proteins can help to maintain the energy required to protonate a site in the protein nearly constant over a wide pH range. We show with the example of RNase T1 that such a mechanism to keep the protonation energy constant is used in enzymes. The pH dependence of pK_a values may be an important concept in enzyme catalysis. Neglecting this concept, important features of enzymes may be missed and the enzymatic mechanism may not be fully understood.

The protein design program MUMBO and its application for the design of discriminative heterodimeric proteins.

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Computational protein design is getting beyond the teenage phase, yet, until today only few computer programs are available that allow for the design of proteins with specific properties. We have developed the computer program MUMBO written in FORTRAN95 and which combines a number of established design algorithms. Based on a rigid backbone approach, side chains are built using either backbone-dependent or independent rotamer libraries. The best combination of amino acids and side-chain orientations is selected using the dead end elimination (DEE) algorithm and variations thereof (pioneered by the Steven Mayo group) [1]. Selection stringency is further enhanced by combining DEE and Monte-Carlo simulated annealing (pioneered by the David Baker group) [2]. The force field includes standard interaction potentials (based on the CHARMM19 parameters), a solvation model [3] and either empirical or geometry-derived estimates for hydrogen bond interactions [4].

In the past we have demonstrated the usefulness of the program MUMBO for the refinement of protein models in crystallography [5] as well as for the docking of substrates into the active sites of enzymes [6]. We have now used MUMBO for the design of specific heterodimeric variants of the bacterial transcription regulator TetR. The goal was to create two different variants A and B that no longer form AA and BB homodimers but which selectively combine to yield heterodimers. To do so, we only had to substitute three residues in one chain and two residues in the second. The designed A and B chains were characterised by producing the proteins recombinantly in E. coli and using an *in vivo* transcription assay. Crystal structure analyses showed that while in case of the BB *versus* AB dimer, selectivity is achieved through van der Waals repulsion, in case of the A chain, selectivity is actually achieved through the under-packing of the interface, which leads to a decrease in thermal stability and a drastic reduction in solubility of the AA homodimer compared to the AB heterodimer.

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TRANSITION-METAL-FREE HYDROGENATION AND HYDROGENOLYSIS: A COMPUTATIONAL APPROACH

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Catalytic hydrogenation is an important chemical reaction in a wide variety of areas, such as industrial processes, organic synthesis, and biological sciences. Most of these reactions are catalysed by transition metal complexes. For example, compounds that contain platinum-group metals have been used extensively in the hydrogenation of fats in the food industry. In microorganisms, catalytic hydrogenation is carried out by enzymes known as hydrogenases, metalloenzymes that normally contains nickel and/or iron-sulfur clusters. Catalytic hydrogenation without transition metals is much less prominent. Among such studies, it has been found that strong acids can be used as catalysts for the hydrogenation of unsaturated hydrocarbons with molecular hydrogen. It has also been demonstrated that zeolites catalyse the hydrogenation of alkenes. Furthermore, it has been observed that some carbonyl compounds undergo catalytic hydrogenation in the presence of a strong base. In recent years, we have been using quantum chemistry computations to examine the fundamentals of transition-metal-free hydrogenation and hydrogenolysis.[1–9] In this presentation, I will describe highlights from our studies in this area.

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Bayesian methods for structure-property modelling

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Detailed atom- or molecule-level modelling studies of complex biological and materials properties have undoubtedly been useful for understanding mechanisms, and for building predictive models. However the very complexity of these systems has also required complementary coarse-grained (mesoscale) pattern recognition approaches to find robust, predictive models that relate the microscopic (atomic and molecular) properties of molecular components to their macroscopic properties.

Well-known examples of this coarse-grained modelling approach include mesoscale representations of polymers and proteins commonly adopted in molecular dynamics calculations[1], multipole representations of ligands for docking[2], and quantitative-structure-activity and structure-property relationships (QSAR/QSPR) methods. The QSAR method has been particularly useful over several decades in providing a simple way of developing predictive models of complex biological properties such as drug efficacy, ADME properties, and toxicity. Modern mathematical techniques such as neural networks, genetic algorithms, and support vector machines have added substantial value to the QSAR method[3].

However, most QSAR models require some form of regression or classification. Such mathematical methods are 'ill posed' and can suffer from instability such as overfitting[4]. In addition, although neural networks are very useful in generating objective, nonlinear QSAR models, they are also prone to overtraining, interpretation, and validation difficulties. Bayesian methods are a powerful adjunct to these very useful regression and classification methods that transform them into mathematically 'well posed' robust methods[5]. Properly applied, Bayesian methods can be used to very effectively select relevant features or descriptors for QSAR/QSPR modelling without the risk of chance correlations, and can provide nonlinear models relating molecular structure to macroscopic properties that optimize the complexity of the models[6,7]. This results in models with the best balance between bias (model too simple and not capturing underlying structure-activity relationship) and variance (model too complex and fitting noise). This paper will describe how Bayesian methods are applied to modelling, and illustrate the performance with data sets.

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Atomistic Molecular Modelling: Applications in Pharmaceutics

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Abstract

Recent work has shown that molecular modelling at the atomistic level has an important role to play in both understanding and designing complex systems of importance in pharmaceutics.

Several examples will be used to illustrate the value of different modelling methodologies by highlighting the key information each method can yield. Examples will include the use of molecular dynamics methods to select materials for use as drug delivery agents, the use of polymers to enhance the dispersion of carbon nanotubes in solution and the design of conducting polymers to aid drug release.

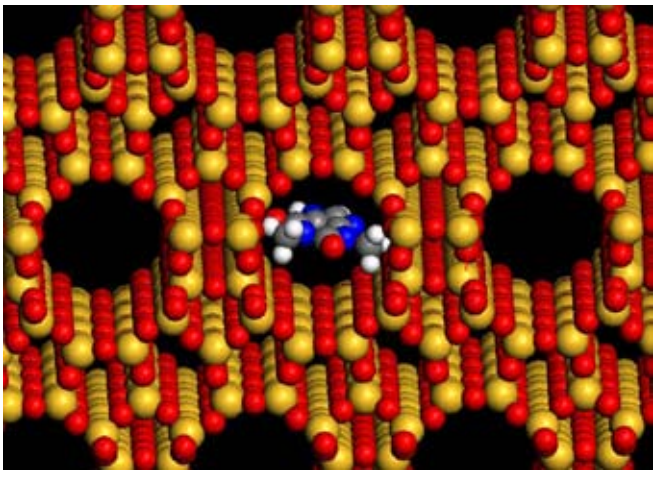

Figure 1: The drug molecule theophylline diffusing through a microporous host.

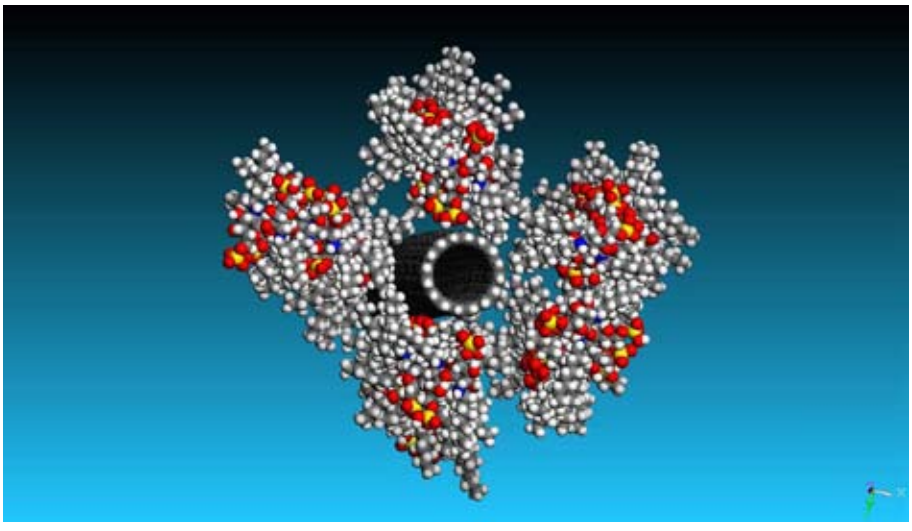

Figure 2: Polymeric molecules can be used to enhance the solubility of carbon nanotubes.

From Ions in Solution to Nanocrystals and Composite Materials: Insights from Atomistic Simulations

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We present a recently developed simulation method for exploring the mechanisms of crystal nucleation from solution. By efficient tackling of the time-length scale problem, molecular dynamics simulations allow very detailed insights into the association of ions from solution and the development of structural motifs resulting in the nucleation of nanocrystals. Our studies of ionic self-organization include ripening reactions, such as proton transfer events and the interplay with growth-controlling molecules. The former issue is illustrated by the example of Zn^{2+} and OH^- association in ethanolic solution, condensation reactions leading to O^{2-} ions and the nucleation of ZnO domains in the aggregate core. The interplay of ionic ordering and growth-controlling molecules is of particular interest for the investigation of composite materials. By the example of biomimetic apatite-collagen models, we demonstrate the design of crystal motifs induced by ion association to the protein fibers.

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The Role of Specific Ion Effects on the Self-Assembly of Structured Polycarboxylate Micelles

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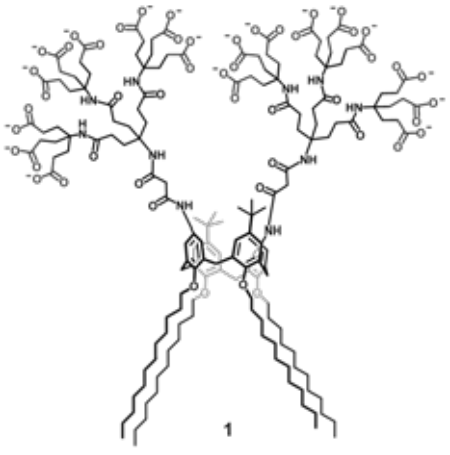
The effect of counterions on the controlled self assembly of structurally persistent micelles has been investigated in detail by long-time-scale atomistic molecular-dynamics simulations and cryo-Transmission Electron Microscopy (cryo-TEM) experiments.



NMR and cryo-TEM investigations of the aggregation behavior of the specifically designed T-shaped amphiphilic calix[4]arene derivative **1** with subsequent 3D-reconstruction of the cryo-TEM images revealed that **1** forms structurally persistent micelles in water.[1,2] These micelles consist of seven or twelve monomers and show a highly conserved topological arrangement of the monomers with almost no tendency to dissociate.

The MD simulations allow a detailed interpretation of the cryo-TEM 3D-reconstructions of the micelles. Several fascinating details of the structure of the solvent around the micelles and the factors that affect the structure of the micelles were revealed.

The simulations first revealed the dominant effect of sodium counterions in stabilizing the known heptameric micelles. This was subsequently confirmed by cryo-TEM experiments. The simulations suggest that the stabilization is due to the formation of strongly conserved hydrated contact ion pairs with sodium but not with potassium.[3]

The factors governing the stability of the micelles will be discussed. In particular the effect of metal cations on the interplay between the hydrophobic effect and the head-group repulsion of the polycarboxylates will be discussed in detail and compared with the second class of larger micelles, which undergo an additional stabilization by hydrophobic guest molecules.

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Density Functional Theory for Fluids at the Nanoscale

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The interplay of thermal noise and molecular forces is responsible for surprising features of liquids on sub-micrometer lengths - in particular at interfaces. Not only does the surface tension depend on the size of an applied distortion [1], but also the dispersion relation of capillary waves differ from the familiar macroscopic behaviour and nanoscopic thin liquid films dewet faster than would be expected from hydrodynamics [2]. Also in equilibrium, fluids open up new astonishing perspectives when confined to small containers. Nanobubbles seem to be more stable than thermodynamically allowed and free energies of confined fluids seem to depend only on four thermodynamically relevant shape variables [3]. This allows the modeling of solvation energies of proteins [4] and of nematic phases in liquid crystals [5]. Some answers to these phenomena can be given by density functional theory, which has become the standard approach to describe fluids at the nanoscale.

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Multiscale Modeling of Biological Functions

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Modeling the function of biological systems is a major conceptual and computational challenge . Using fully atomistic models with rigorous simulation treatments might prevent one from reaching clear conclusions about the action of the given system , whereas the construction of oversimplified models without sufficient physical basis might lead to irrelevant conclusions . This talk will review our progress in multiscale modeling, emphasizing the physical reality and the connection between the different modeling levels. We will start with a brief description of simplified folding models (1) ,which are perhaps the first examples of multiscale (Coarse Grained (CG)) modeling in studies of proteins, and describe a connection between the simplified and the all atom models (2) . We will then consider very briefly QM/MM calculations (3,4) of proteins, which also provide examples of multi scale studies. Next we will move to the main topic, which will be the demonstration of the use of consistent multiscale modeling of ion current in ion channels and of the action of proton pumps. In both cases we will explain how can one moves from a fully atomistic microscopic treatment (sometimes with quantum mechanical elements) to semimacroscopic free energy surfaces and eventually to Brownian Dynamics or Monte Carlo simulations of slow events (5,7). We will thus provide examples of consistent simulations of millisecond biological processes using various multiscale strategies .We will also demonstrate the use of CG modeling in enzyme design and related problems (8).

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Molecular Dynamics Simulations and Signal Transduction

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The tetracycline repressor TetR is in many ways representative for signal-transduction proteins. It can be used as a switchable gene regulator for both eukaryotic and prokaryotic organisms, which encouraged many structural, mechanistic, and theoretical investigations.

Molecular dynamics simulations on several variants (normal and reverse phenotype) of TetR, both in the absence of an inducer and complexed with the inducers tetracycline and 5a,6-anhydrotetracycline, show significant differences in the structures and dynamics of the induced and non-induced forms of the protein. In this talk, I will discuss how we can use MD simulations to gain atomistic insight into the mechanism of induction of this important class of regulatory protein complexes.

DNA Polymerase Fidelity and Human Telomeric Quadruplex Conformations

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Molecular dynamics simulations on two different systems will be presented. The first is a mutant of DNA polymerase I from Thermus Aquaticus (Taq) with higher fidelity compared to the wild type. The accurate replication of DNA is of the utmost importance for the maintenance of genomic integrity. Polymerases have evolved a very high fidelity with error frequencies of approximately one in 10^3-10^6 bases synthesized. The even better mutant was identified by an efficient automated high-throughput setup for the rapid parallel screening of mutant libraries [1] developed to respond to the demands of numerous biotechnical applications like polymerase chain reactions (PCR) with their unnatural conditions. Simulations of Watson-Crick and mismatched incoming deoxyribonucleoside-triphosphates show that the high fidelity of the mutant can be partly explained by different specific interactions between amino acids of the enzyme and the DNA primer end as well as, in some mismatches, a displacement of the primer relative to the incoming nucleotide and the catalytic magnesium ion [2].
Guanosine-rich nucleic acids are known to fold into four-stranded structures called quadruplexes Particular sequences, namely the telomeric repeats at the end of the chromosomes, have generated much interest. Due to the potential to switch between folded and unfolded state, the formation of quadruplex structures is suspected to play important roles in telomere maintenance and cell cycle control. The human telomeric repeat is known to adopt drastically different conformations depending on parameters such as the type of monovalent ions coordinated by the guanine tetrads and the nature of the examined sequence. Long-range distance measurements by spin-label EPR for investigating quadruplex structures suggest the presence of a 1:1 mixture of a parallel propeller and an anti-parallel basket structure in K^+ solution [3]. Molecular dynamics calculations show that it is really possible to discriminate between these structures by the EPR-based distance measurements, so that they can be used to identify and quantify structural mixtures of DNA or RNA quadruplex with respect to experimental conditions.

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Computer Simulations of Processes Involved in mRNA Translation on the Ribosome

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We will present an overview of our recent calculations on the different processes involved in mRNA translation on bacterial ribosomes. Key topics such as the peptidyl transfer step in the elongation reaction and peptidyl-tRNA cleavage in termination of protein synthesis will be discussed. We will also address the mechanism whereby ribosomal release factors are able to specifically recognize stop codons.

Influence of Anesthetics on Membranes and Membrane Proteins: Implications for Anesthesia

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Although anesthesia is widely used in clinical applications, the underlying molecular mechanisms are not yet known. It is generally assumed that anesthetics act by either binding specifically to membrane proteins, or by changing the properties of biological membranes involved in signal transduction, thereby affecting the function of embedded proteins indirectly.

Here, the effect of 1-alkanols of different chain lengths — some of them anesthetics, others not — on the lateral pressure profile across pure dimyristoylphosphatidylcholine (DMPC) bilayers was studied by long-term molecular dynamics (MD) simulations. The simulations were performed at normal and enlarged external pressure to elucidate also the experimentally demonstrated pressure reversal of anesthesia, i.e. the effect that anesthesia in animals can be reversed by external pressures between 70 and 350 bar. It is shown that 1-alkanols and external pressure may shift conformational equilibria between hypothetical open and closed states of membrane proteins in opposite directions.

In addition, the influence of some anesthetics on an ion channel–membrane system was investigated using MD simulations. We found a strong decrease of drug adsorption close to the embedded ion channel (gramicidin). In agreement with lipid-mediated theories, the drug molecules influence both the structure and dynamics of the ion channel by modulating the properties of the surrounding lipid environment. Ethanol decreased the pore radius coupled to an increase in protein fluctuations while decanol increased the pore radius.
In summary, our results lend support to Cantor's model that anesthesia is mediated by local pressure changes in the membrane and probably not by specific binding to ion channels.

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Mean field Methods abused and confused – RNA base pairing and design

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RNA structural calculations have long suffered under the tyranny and cruelty of computer scientists. Firstly, the molecule is usually regarded as being two-dimensional. Next, base-pairs are usually predicted with dynamic programming methods that are fast, but only because they search an embarrassingly small subset of possible solutions (ignoring pseudoknots). Finally, the most popular energy functions are so ugly, they would cause a dead computational chemist to turn in his or her grave.

For the moment, we are also calculating in a two-dimensional world and we have not done anything about the beauty of the energy functions. We have, however, used mean-field methods to predict optimal base-pairings. The result is a method which can find good base-pairs in terms of the way the problem is posed and . The bad news is that they may not be entirely believable and suggest that popular energy terms are as evil as a room full of North Korean presidents.

Fullerenes and nanotubes see the light (!)

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Multifunctional carbon nanostructures are currently under active investigation for producing innovative materials, composites, and optoelectronic devices, whose unique properties originate at the molecular level. Among the wide variety of carbon allotropes recently discovered, C_{60}, single wall carbon nanotubes (SWNT) and single wall carbon nanohorns (SWNH) are of particular interest. C_{60} is entirely made of pentagons and hexagons resulting in 0.78 nm sized truncated icosahedral carbon spheres. In contrast, the structure of SWNT has a cylindrical shape, which can be conceptually generated by wrapping a one-atom-thick layer of a graphene sheet into a seamless cylinder. The diameter of most SWNT is around 1 nm – similar to that of C_{60} – with a tubular length that can reach many thousands of times their diameter. Importantly, based on different arrangements, SWNT possess different electrical properties, which are the result of the electrons moving differently in the tube depending on the SWNT arrangement. SWNH, on the other hand, are typically constituted by tubes of about 2-5 nm of diameter and 30 to 50 nm long, which associate with each other to give rise to round-shaped aggregates of 100 nm of diameter. Their large surface areas and inner nanospaces are of great importance, since they ensure a great affinity, for example, with organic electron donors.

The accomplishment of multiple-performance objectives in a single system necessitates combining these carbon allotropes with other classes of materials. Our past work has mapped out compounds that proved particularly useful: active organic materials such as porphyrins / phthalocyanines and oligomers / polymers. We have demonstrated that linking these molecular building blocks creates enormous synergisms in going much beyond just harnessing the features of the individual subunits or constituents. Eventually it enables the control over molecular arrangement – well-defined ensembles and superstructures with widely differing property values – and results in the development of the necessary tools for fine-tuning properties on the molecular, nanoscale level.

I will highlight the opportunities that rest on fullerenes and single wall carbon nanotubes within the context of charge transfer reactions in novel chemical as well as light driven systems with high tensile strength. A fundamental aspect of our research is to integrate such functions without sacrificing the structural and electronic integrity of the material. In this context, I will survey our concepts to generate functional entities using the bottom up approach, that is, to design, manipulate, characterize, examine, and understand the potential of carbon materials as a novel platform for stable electron donor-acceptor hybrids and conjugates. Important aspects will include the impact, the benefits and some of the promises that evolve from charge transfer reactions involving carbon nanostructures with high tensile strength on i) the stabilization of radical ion pair states, ii) multi electron catalytic reactions, and iii) photoelectrochemical / photovoltaic solar energy conversion.

Atomistic simulations for complex systems with chemical accuracy

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(August 10, 2009)

With recent advances in both, experiment and computer simulations, it has become possible to investigate the dynamics of small molecules in heterogeneous environments. This is of particular interest because small ligands can be used as an experimental probe to investigate the interior of proteins or other disordered materials.

Atomistic Simulations are an established computational method to investigate gas- and condensed-phase systems. Recent extensions to force fields incorporate more details in capturing electrostatic interactions and allow to more quantitatively understand particular processes. Here, I will describe some of these methods and their use to understand the energetics, [vibrational]spectroscopy and reactions in biological and physico-chemical systems. For myoglobin interacting with diatomic ligands the vibrational spectroscopy of the ligand[1,3,4,5] and its rebinding kinetics are long-standing problems in biophysics which continue to attract the attention of experimentalists and computational chemists. The relationship between spectroscopy and structure is an interesting problem in the physical chemistry of doped ices which play an important role in astrophysics.[2,3]

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Ions at Aqueous Interfaces: From Water Surface to Hydrated Proteins

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Surfaces of aqueous solutions are traditionally viewed as devoid of inorganic ions. Molecular simulations and surface selective spectroscopic techniques show, however, that large polarizable anions and hydronium cations can be found (and even enhanced) at the surface and are involved in chemistry at the air/water interface. Here, we present recent studies of ions at the water/vapor interface and compare from this perspective more complex aqueous interfaces, such as those of hydrated proteins. We critically examine the suitability of dielectric models for the description of the protein/water interface in analogy to the water/vapor interface. Little correlation is found between these two interfaces in terms of ion segregation. Therefore, a local picture of pairing of ions from the solution with charged and polar groups at the protein surface is advocated and combined with a model for segregation of large soft ions at hydrophobic patches of the protein surface.

Membrane Transport Proteins - an understudied class of drug targets

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Structure and Dynamics of Alzheimer's $A\beta_{42}$-Amyloid Oligomers

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Converging lines of evidence suggest that soluble Aβ-amyloid oligomers play a pivotal role in the pathogenesis of Alzheimer's disease, and present direct effectors of synaptic and cognitive dysfunction. To address the effect of the oligomerization state on Aβ structure, we performed systematic molecular dynamics simulations of 0.5 μs in total on five $A\beta_{42}$ oligomers (monomer through pentamer). While the conformation of the trimer to pentamer remains similar to the fibril structure, the dimer forms a distinct barrel-like structure with mixed β-sheets shielding a hydrophobic core. The fact that the dimer predominantly exists in conformations clearly distinct from the fibril may offer an explanation for dimer stability and neurotoxicity.

The present study also assessed the effect of four pathogenic mutations at position 22 from 20-ns molecular dynamics simulations and subsequent structural and energetic analyses. Our data shows that E22 plays a unique role in wildtype Aβ, since is has a destabilizing effect on the oligomer structure due to electrostatic repulsion between adjacent E22 sidechains. Consequently, mutations, which replace E22 by a non-charged residue, result in higher oligomer stability. The effect is also observed for lesser extent for the E22K mutation and is consistent with the lower pathogenicity compared to other mutants. Interestingly, the deletion of E22 does not destabilize the amyloid fold but is compensated by local structural rearrangements including changes of dihedral angles and the formation of alternative hydrogen bonds at the site of mutation. The finding that all mutants investigated exhibit a higher internal stability than the wildtype offers an explanation for the experimentally observed enhanced oligomer formation and stability. The correlation between internal stability, aggregation tendency and pathogenicity and might be helpful for the design of drugs targeting small but toxic Aβ-amyloid compounds.

RNA based molecular machines and enzymes. Theory and experiment.

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RNA molecules are characterized by astonishing variability of molecular interactions. While the biology of RNA is being rapidly discovered, the understanding of physics and physical chemistry of RNA is lagging behind, and in this area computations can help. Computational techniques such as explicit solvent molecular dynamics (MD) and quantum chemistry (QM) can fill some of the many gaps in our knowledge (1,2). Computational techniques have numerous limitations and are notoriously prone to over-selling and misuse (1,3). Nevertheless, when properly applied, computations can provide data that cannot be harvested by other techniques (1-3). Thus, MD can classify strikingly variable structural flexibilities of RNA building blocks which are of functional importance for stochastic biomolecular machines (4,5). MD is instrumental in studies of long-residency hydration that can be of structural (1), dynamical (4,5) and catalytic relevance (6). Simulations can map major binding sites of (monovalent) cations including those that are delocalized (1,3). MD is efficient in testing effects of base substitutions and modifications, including variable protonation states. QM techniques are primarily designed to investigate the nature and magnitude of molecular interactions in nucleic acids and provide link between molecular structures and energies (7,8). Proper application of computational methods requires close cooperation with bioinformatics and experiment. I will briefly summarize advantages, limitations and areas of application of these methods, and illustrate their relation with structural bioinformatics, crystallography, cryo-electron microscopy and biochemistry for ribosome and ribozymes. The examples will include dynamical functional centers of ribosome, structural dynamics and chemistry of catalytic centers of ribozymes, and classification of structures, energetics and evolutionary patterns of molecular interactions in RNAs.

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Molecular flexibility and molecular recognition in nucleic acids

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I will discuss some of our recent work looking at how protein-DNA and ligand-DNA interactions are modulated by changes in nucleic acid flexibility. Specifically, I will describe our recent investigations of how formamidopyrimidine-dG (FapydG) lesions change local DNA flexibility and how this may contribute to selective recognition by the repair protein FPG. I will then describe our latest work investigating methodologies for the accurate prediction of the sequence-selectivity of DNA minor groove ligands, where again subtle changes in DNA flexibility with sequence may play a key role in modulating affinity.

Theoretical investigations of DEA-NONOate decomposition pathways

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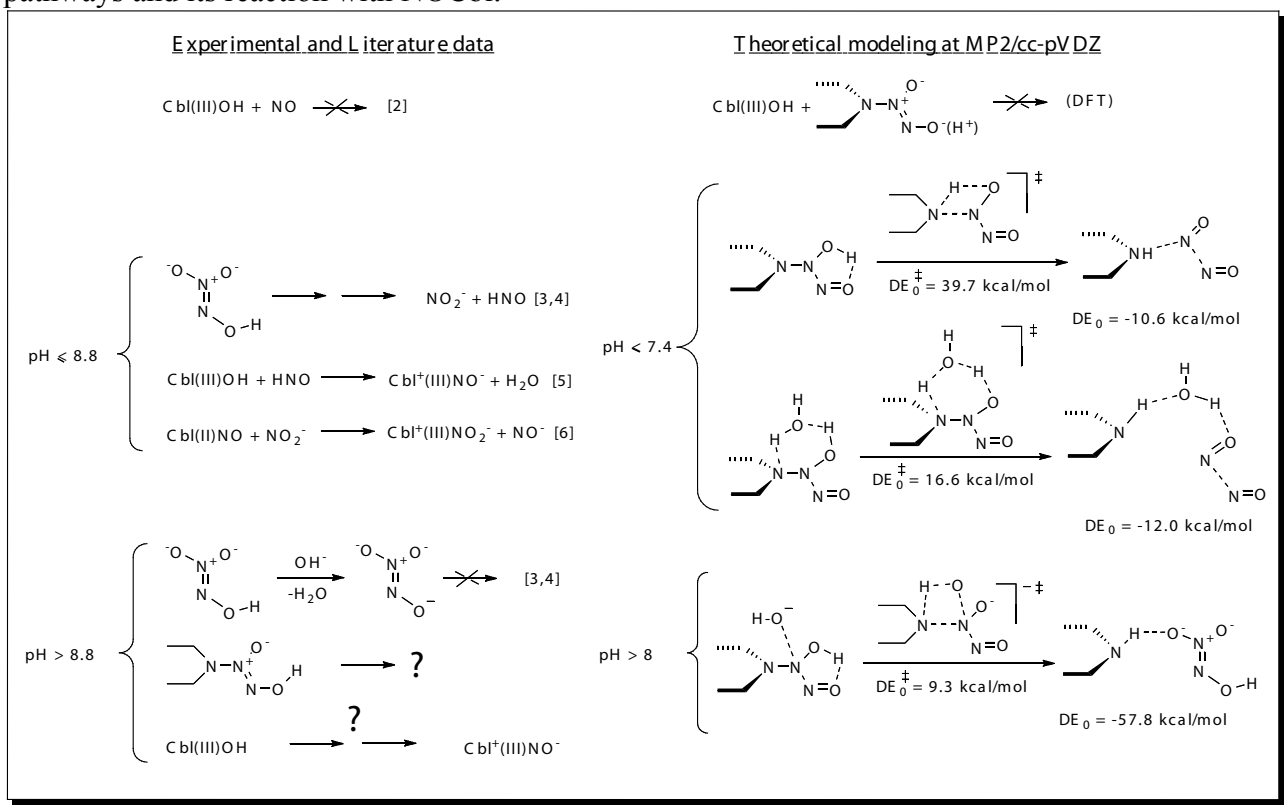
Nitric oxide (NO) is an important bioregulatory agent, and structural studies of the interactions of hemes and heme models with NO have played a major role in elucidating the activation mechanism of the NO-receptor enzyme guanylate cyclase. Emphasis has also been placed on various NO carriers and how such entities function to release NO. Previously it was shown that the Drago $R_2N[N_2O_2]^-$ anions ("NONOates") are smooth nonenzymatic releasers of nitric oxide in physiological media.

The NO derivative of vitamin B12, known as nitrosylcobalamin (NOCbl), has recently attracted a lot of attention in the literature. The first efficient procedure to synthesize NOCbl was reported in 2007 and was based on reaction of the NO donor 2-(N,N-diethylamino)diazenolate-2-oxide (DEA-NONOate) with hydroxycobalamin hydrochloride.[1]

Provided the importance of the understanding mechanisms of such reactions, we have preformed extensive DFT and MP2 calculations on possible DEA-NONOate decomposition pathways and its reaction with NOCbl.



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Modeling of water oxidation in photosystem II and proton pumping in cytochrome oxidase

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Hybrid density functional theory has been used to study the mechanisms of a large number of transition metal containing enzymes. The present strategy for treating these systems will be described, with comparison of large DFT and QM/MM models. DFT studies on the mechanism for dioxygen formation in photosystem II is then described. After the first X-ray structures of PSII appeared a few years ago, the understanding of this fundamental reaction has improved significantly. A detailed mechanistic proposal will be presented including a complete energy diagram. During the past year major progress has also been made concerning the structure of the oxygen evolving complex. It will be argued that the theoretical prediction of the structure is at present more accurate than, and even qualitatively different from, what is obtained by X-ray crystallography. Finally, a mechanism for proton pumping across the membrane for cytochrome c oxidase will be presented. Quantitative reasoning, rather than large calculations, has been particularly fruitful in this case.

Developing and validating modern DFT methods for modelling complex systems. From mixed-valence systems to local hybrid functionals

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Computational Uranyl Chemistry: Heavyweights in Silico.

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Recent progress in the application of Car-Parrinello molecular dynamics (CPMD) simulations to uranyl(VI) complexes is reviewed. Special attention is called to the speciation of aqueous uranyl(VI) complexes with water and halide, nitrate, or pertechnetate ligands. Coordination numbers about uranyl, the binding mode of chelating ligands, monodentate vs. bidentate, as well as the mechanism of ligand exchange are assessed in terms of free energies computed from suitable thermodynamic integration schemes. According to these simulations, pertechnetate should bind less strongly to uranyl than nitrate [1], and the affinity of the tetrafluoride to bind an additional water ligand affording $[UO_2F_4(H_2O)]^{2-}$ (eq 1) is much lower than hitherto assumed [2]. The role of counterions in stabilizing such a five-coordinate species in the solid state [3] and in aqueous solution is discussed.

(1)

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A Quantum of Common Sense in Protein Crystallography

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The starting point for structure-based drug design (SBDD) efforts is a high quality structural model obtained using X-ray crystallography or NMR spectroscopic techniques. Recently, it has become clear that many available protein/ligand complexes have structural inconsistencies that limit their usefulness in developing and validating SBDD tools like docking and scoring methodologies. In most instances classical tools are used as structural surrogates in X-ray and NMR refinement protocols in order to improve the parameter to observation ratio realized from these experimental techniques. While classical approaches are useful structural surrogates, they do suffer from a number of issues that affect their performance including: electrostatic modeling, parameter defects and missing parameters. The way in which these issues can be mitigated is to use more robust structural theories like quantum mechanical (QM) methods, which have had a tremendous impact on our understanding of "small" chemical and biological systems. In this presentation we will focus on some of the first applications of *ab initio* QM methods to refine protein/ligand complexes for use in SBDD applications. In our first example, we will describe the use of computational NMR spectroscopy tools to place or "pose" ligands in the active site of a protein, while in the second example we will discuss the use of QM in X-ray structure refinement. Finally, we will briefly summarize our vision of the future application of quantum chemistry to structure refinement as well as SBDD.

Anti-Target Optimization in Medicinal Chemistry: Do in silico tools help?

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Pharmaceutical drug research is a multi-objective optimization problem not only concerned with potency, efficacy, and selectivity, but additionally with finding a suitable compromise also by reducing physicochemical and pharmacokinetic liabilities of early hits.

Phaenomenological models that describe chemical features responsible for a pharmacological effect and provide an optimization rationale are highly desired over classical black box QSAR models that connect molecular descriptors with some target property. Nevertheless, fast and effective alerts with about eighty percent accuracy can be obtained by classical QSAR and allow for priorization within HTS analysis, compound purchase and virtual compound profiling datasets, when applied in the context of clusters and not taken literally for any specific compound.

Most important for predictive models are high quality data sets. These should be acceptably large, internally diverse and with similar profile to the warehouse to predict. With our dataset for human serum albumine binding it is not only possible to create a highly predictive HSA model but also an satisfactory model for fraction unbound in human as derived from caclulated HSA.

On the other hand, the dataset used for the creation of CypScore as a tool for the prediction of cytochrome P450 mediated metabolic lability prediction is much smaller, but favorably matches the observed variety of metabolic reations. CypScore is presented as an example for a phaenomenological model, based on specific AM1 quantum-chemical atomic reactivity models for the most important phase-I reactions. Instead of a diffuse metabolic stability value, it hints to the most attractive molecular regions for chemical modifications.

The dataset avaible to us for hERG inhibition is much too limited to create global models of the quality needed for lead optimization. topoHERG, a knowledebase approach for the classification of hERG inhibition based on pharmacophore-similarity which allows to learn from successful chemical modifications in near neighborhoods, is presented as a proof-of-concept study that currently lacks from the small structural data basis. topoHERG is compared with decision tree and SVM black box models with larger applicability domain but lower accurcy.

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Active site motions and catalysis in Formyl-CoA:oxalate transferase

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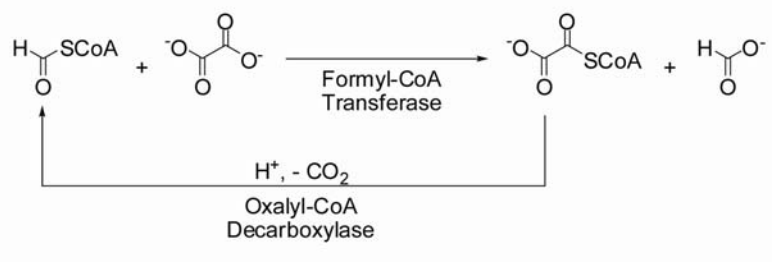
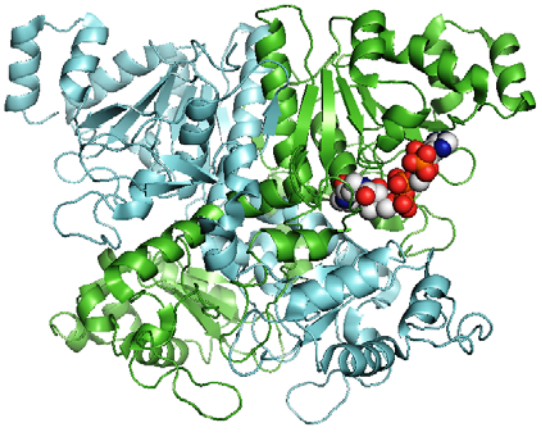
Oxalate is the primary energy source for *Oxalobacter formigenes*,[1] a bacterium that is present in the gut of several mammalian species including humans.[2] There is a striking correlation between the absence of this microorganism and kidney stone disease,[3] perhaps because *Oxalobacter* plays a symbiotic role in controlling oxalate homeostasis in humans.[4] Oxalate is converted into formate and CO_2 in a catalytic cycle that is mediated by two enzymes: oxalyl-CoA decarboxylase[5] and formyl-CoA transferase.[6] The active site of the latter lies at the interface of two monomers in the "interlocked" homodimer,[7] and X-ray crystal structures have been obtained for several intermediates in the acyl transfer mechanism showing conformational changes that must take place to mediate catalysis.[8] In addition to outlining the consequences of these structural alterations for catalysis, normal-mode analysis (NMA) calculations[9] to evaluate the extent to which these motions are a consequence of intrinsic protein dynamics will be described. These computational studies also provide new insights into how global, low-frequency protein motions may act to correlate catalysis in the two active sites.





(Left) Oxalate degradation in bacteria. (Right) A cartoon representation of the formyl-CoA transferase/coenzyme A complex, showing the location of the active site between the large and small sub-domains of monomers A and B, respectively. Protein monomers are shown in green or blue ribbon representations. Bound coenzyme A in the active site is rendered in a space-filling representation, and atoms are colored according to the following scheme: C, grey; N, blue; O, red; P, purple; S, yellow.

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The importance of methionine and of a Tyr/Asp diad in prenyl transferases and terpene synthases

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Prenyltransfering enzymes are at the basis of the vast isoprenoid natural product diversity. They include, e.g., aromatic prenyl transferases, prenyl diphosphate and terpene synthases, all of which activate an (olig)prenyl diphosphate to form a stabilized prenyl cation reactive intermediate, that after addition to a nucleophile (C=C bond) and deprotonation delivers the product(s). So far, aromatic amino acids have been suggested to stabilize the cation intermediate. In this paper their role is elucidated further, but most importantly, other nucleophilic amino acids, specifically methionine are suggested as additional or alternative aids for cation stabilization. This suggestion is supported by site directed mutagenesis, bioinformatics and modelling studies. In addition, a new catalytic diad composed of Tyr and Asp, represented by a Yx(x)xxD-motif, is identified as important player for deprotonation and proton-relay in intermediates and finalizing deprotonation steps of many prenyl transferring and cyclizing enzymes.

Utilizing the Catalytic Machinery of Lipases for Promiscuous Activities

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The last decades of biocatalytic research has demonstrated that enzymes often can use alternate catalytic mechanisms and catalyze more than one chemical transformation. Such catalytic promiscuity, which is inherent to many biocatalysts, may be utilized in the redesign of enzymes to obtain new catalytic activities. We have found the catalytic machinery of serine hydrolases particularly suited for the transformation of carbonyl compounds. Using a combination of quantum chemical calculation and molecular dynamic simulations, we have shown that mutating a single residue, the catalytic serine, in Candida antarctica lipase B (CALB) results in an enzyme that can catalyze a number of reactions important in organic synthesis, including, aldol addition, Michael type additions and epoxidation [1-4]. In addition, the mutant shows no activity for the natural reaction of CALB, i.e. ester hydrolysis.

In this lecture we will demonstrate that the catalytic promiscuity of lipases also extends to reactions of compounds with a nitrile functionality. In particular we will report on catalysis of carbon-carbon bond formation/breaking in nonpolar environments. Molecular dynamics (MD) simulations show that solvents of low polarity induce structural changes in the active site geometry that result in substrate binding and activation. Subsequent quantum chemical calculations based on the MD structures reveal the details of the catalytic mechanism. The computational results together with experimental findings indicate that the entire catalytic machinery of the lipase, including both the catalytic triad and the oxyanion hole, participates in the catalysis of the promiscuous reaction.

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COMPUTATIONAL STUDIES ON ORGANO(METALLIC) REACTION MECHANISMS

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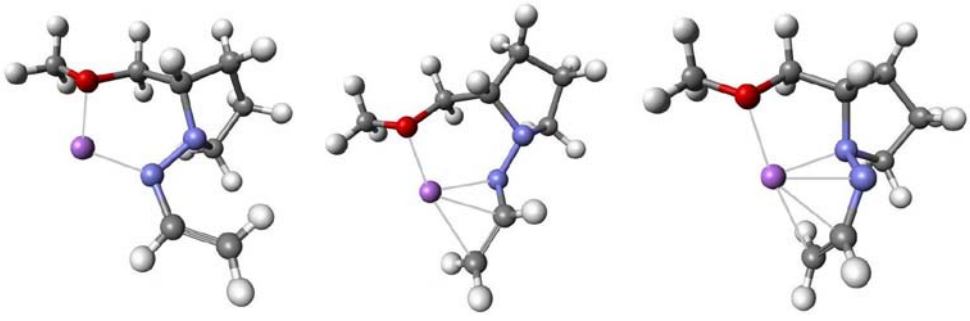
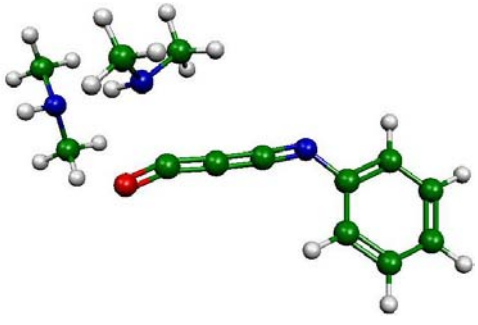
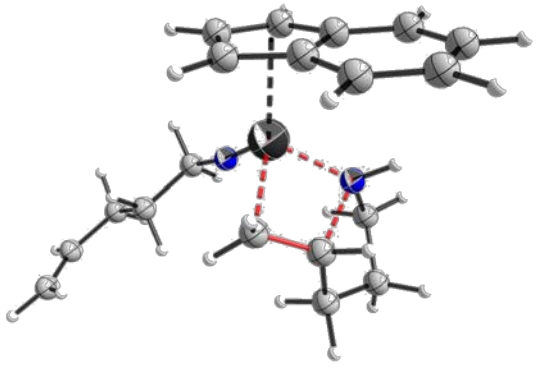
This talk deals with the application of mainly density functional and perturbation theoretical methods for the elucidation of reaction mechanisms. It covers the range of stereoselective reactions over reactive intermediates to catalytic cycles.
The asymmetric SAMP-assisted C-C bond formation, a synthetically successful reaction for several decades now, is investigated for the first time. Both a proposed mechanism as well as the semiquantitative prediction of the stereochemical outcome is presented.



Iminopropadienones, reactive heterocumulenes formed in flash vacuum pyrolysis, can react at very low temperatures with nucleophiles to yield regiospecific products.



Another example is the early transition metal complex-catalysed hydroamination of alkenes.



The Reaction Force

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The reaction force **F**(**R**) is the negative gradient of the potential energy V(**R**) of a chemical process along its intrinsic reaction coordinate **R**. **F**(**R**) normally has one or more maxima and/or minima which represent a natural division of the process into regions. Some of these are dominated by structural changes in the reacting system, while others feature electronic as well as structural factors.[1] Since activation barriers include contributions from both types of regions, it is possible to determine whether the effects of catalysts, solvents, etc. are primarily structural or electronic.[1,2] **F**(**R**) defines a "transition-to-products" region, which is characterized by the reaction force constant [the second derivative of V(**R**)] being negative throughout its entirety, not just at the maximum of V(**R**).[3] This is consistent with the concept of a continuum of transient states that comes out of transition state spectroscopy.[4]

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Cation Affinity Numbers in Organocatalysis Research

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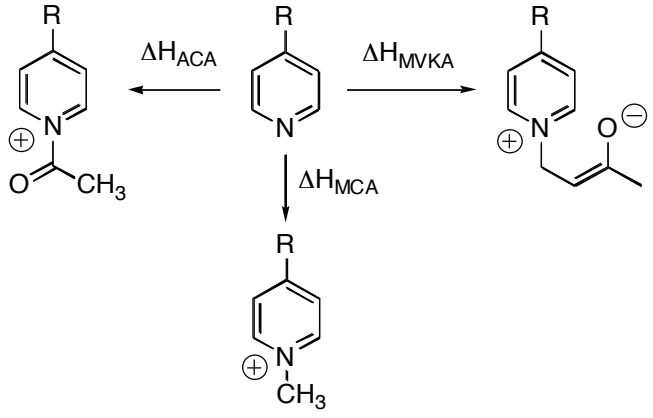
The acceleration of a variety of group transfer reactions by Lewis bases such as amines and phosphines represents an important part of the field of contemporary organocatalysis, with particularly interesting applications in the area of stereoselective transformations. In recent years simple affinity numbers such as the affinity towards methyl cations (MCA) or the affinity towards acetyl cations (ACA) have been used to rationalize the catalytic performance of known pyridine bases and predict new, more highly active catalysts.[1-3] These studies have also been extended to include prochiral cation probes.[4]



A good number of organocatalytic transformations involve the intial reaction of neutral nucleophilic catalysts with neutral electrophiles, generating zwitterionic intermediates as the first discrete species in the catalytic cycle. Using methyl vinyl ketone (MVK) as a sample electrophile we have now evaluated theoretical methods suitable for the calculation of the corresponding affinity numbers, and have also explored the correlation of such affinity values with those derived for cationic electrophiles.

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