MOLECULAR MODELLING WORKSHOP 2014

Computer-Chemie-Centrum
Nägelsbachstr. 25
91052 Erlangen
Germany

Monday, March, 17th - Wednesday, March 19th 2014

Once again, we in CCC are happy to welcome you to the Molecular Modelling Workshop 2014. This year, it is the 28th Molecular Modelling Workshop and the twelfth time it was hosted by the University of Erlangen-Nuremberg. The research group of Prof. Tim Clark at the CCC will be responsible for the technical organization. Prof. DDr. Klaus R. Liedl and Dr. Christian Kramer from the University of Innsbruck, will be responsible for the scientific organization.

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

Scientific program

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DEAR COLLEGUES,

The 28th Molecular Modelling Workshop (March, 17th - 19th) in Erlangen provides research students and new postdoctoral scientists the perfect opportunity to present their research to the molecular modelling community. Scientists at the beginning of their academic careers are able to meet new colleagues in academia and industry.

Every year, the organisers welcome both poster or lecture contributions in English or German from all areas of molecular modelling including life sciences, physical sciences, material sciences and the nano sciences.

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

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

Our plenary speakers this year are (in alphabetical order):

JOHN D. CODERA PH. D.

Computational Biology Program
Memorial Sloan-Kettering Cancer Center

DR. CHRISTOFER TAUTERMANN

Boehringer-Ingelheim
Biberach / Germany

AWARDS

As in the past years, there will be Awards for the two best posters and three best talks:

POSTER AWARDS

The presenters of the two best posters will be awarded with 100 € each.

LECTURE AWARDS

Winner

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

2nd Winner

up to 200 € travel expenses reimbursement

3rd Winner

up to 100 € travel expenses reimbursement

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

MGMS-DS E.V. ANNUAL MEETING

The general meeting of the MGMS (German Section) will be held during the workshop. We invite all conference delegates to participate in the annual meeting of the society.

FEES

The conference fee amounts to 50 € (Students: 25 Euro€). If you do not disagree, this fee includes the annual membership fee for the MGMS-DS e.V.

JOHN D. CHODERA PH. D.

The Chodera lab uses computation and experiments to develop quantitative, multiscale models of the effects of small molecules on biomolecular macromolecules and cellular pathways. To do this, the group utilizes physical models and rigorous statistical mechanics, with the overall goals of engineering novel therapeutics and tools for chemical biology, as well as understanding the physical driving forces behind ligand recognition the evolution of resistance mutations.

The group makes use of advanced algorithms for molecular dynamics simulations on graphics processing units (GPUs) and distributed computing platforms, in addition to robot-driven moderate and high-throughput experiments focusing on characterizing biophysical interactions between proteins and small molecules.

DR. CHRISTOFER TAUTERMANN

Christofer Tautermann studied Chemistry (MSc 1999) and Mathematics (MSc 2000) at the University of Innsbruck (Austria). For his PhD thesis in computational chemistry (supervisor Prof. Klaus Liedl) he worked on the investigation of proton transfer reactions in small organic systems, but also in enzymatic catalysis. After obtaining a PhD at Innsbruck University in 2003 he went to Oxford (UK) for 2 years to do a PostDoc with Prof. David Clary (FRS), investigating heterogeneous catalysis in ammonia synthesis by theoretical means. In 2005 Christofer joined Boehringer Ingelheim in Biberach (Germany), where his fields of work comprises computer aided molecular design, with a special focus on GPCR modelling. Since 2011 Christofer is head of a team within Computational Chemistry responsible for project support. Christofer is (co-)author of about 50 publications in computational and medicinal chemistry.

Program

PROGRAM

Monday, March 17th 2014

11:30-14:00	**Registration**
14:00-14:15	**Welcome remarks / Agenda review**
14:15-14:40	**Johannes Margraf (Erlangen)** The electronic structure of amorphous and graphitic carbon nanoparticles
14:40-15:05	**Thibaud Etienne (Nancy)** A quantitative assessment of electronic transitions' charge-transfer character
15:05-15:30	**Dzmitry S. Firaha (Bonn)** CO_2 absorption in protic ionic liquids
15:30-15:55	**Philipp Ectors (Erlangen)** Nucleation of molecular crystals
15:55-16:15	**Coffee Break**
16:15-16:40	**Dr. Samo Turk (Heidelberg)** Scaffold Analysis in Python with RDKit and pandas
16:40-17:40	**Plenary Lecture I:** **Prof. John Codera (New York)** Redesigning Drug Design
17:40-18:45	**Annual Meeting of the MGMS-DS**
19:00	**Buffet - Dinner**

PROGRAM

Tuesday, March 18th 2014

08:30-08:55 **Tanaporn Uengwetwanit (Halle)**
Optimization of post-docking strategies for hit identification of HCV NS5B polymerase inhibitors

08:55-09:20 **Dr. Hari Narayana Moorthy (Porto)**
Binding Mode prediction of HMG-CoA Reductase Inhibitors Using Molecular Modelling Tools

09:20-09:45 **Katra Kolšek (Ljubljana)**
An Open Source Prediction Tool for Assessing Endocrine Disruption Potential through Nuclear Receptors Binding

09:45-10:10 **Dr. Birgit Waltenberger (Innsbruck)**
Pharmacophore-based discovery of novel inhibitors of the innovative therapeutic target soluble epoxide hydrolase (sEH)

10:10-10:30 **Coffee Break & Conference Photo**

10:30-10:55 **Berin Karaman (Halle)**
Development and validation of MM-(GB)SA models for predicting the biological stability of sirtuin inhibitors

10:55-11:20 **Adriana Supady (Berlin)**
First-principles molecular structure search with a genetic algorithm

11:20-11:45 **Christian Hanke (Düsseldorf)**
A marginal stability is required for the guanine-sensing riboswitch to function

11:45-13:00 **Lunch**

PROGRAM

Tuesday, March 18th 2014

13:00-13:25	**Birgit Waldner (Innsbruck)** Explaining protein-protein interfaces in protease recognition with local dynamics and local interaction potentials
13:25-13:50	**Francesca Vitalini (Berlin)** Speed of Force Fields: Kinetic Comparison of Force Fields in Biological Systems
13:50-14:15	**Elke Haensele (Portsmouth)** DASH: Analysis of microsecond molecular dynamics trajectories
14:15-14:35	**Coffee Break**
14:35-15:35	**Poster Session I**
15:35-16:00	**Stefania Monteleone (Innsbruck)** Modeling and Molecular Dynamic Simulations of Calcium Channel Voltage Sensor
16:00-16:25	**Christian Wick (Erlangen)** Self-Consistent Field Convergence for Proteins
16:25-16:50	**Florian Mrugalla (Dortmund)** An Integral Equation theory for ligand design
16:50-17:50	**Plenary Lecture II:** **Dr. Christofer Tautermann (Biberach)** GPCR structures in drug design: a case study on the residence time of antimuscarinic drugs
18:30	**Steinbach Bräu**

PROGRAM

Wednesday, March 19th 2014

08:30-08:55	**Antoine Marion (Nancy)** Improving Semi Empirical (NDDO) methods for Born-Oppenheimer Molecular Dynamics
08:55-09:20	**Andriy A. Kazantsev (Kiev)** Conformation-related tautomeric shift in 5-formylcytosine
09:20-09:45	**Heike Thomas (Erlangen)** Parameterization of the hpCADD NDDO-based Polarizable Force Field: The NDDO Hamiltonian
09:45-10:05	**Coffee Break**
10:05-11:05	**Poster Session II**
11:05-11:30	**Tina Kollmann (Erlangen)** Theoretical characterization and synthesis of gelatin based magnetic hydrogels
11:30-11:55	**Dr. T. Steinbrecher (Mannheim)** Large Scale Free Energy Calculations on Congeneric Ligand Series – Applying FEP in Practical Drug Design
11:55-13:00	**Lunch**
13:00-13:35	**Prof. Thorsten Koslowski (Freiburg)** Sensing Organic Molecules by Charge Transfer through Aptamer-Target Complexes: Theory and Simulation
13:35-14:10	**Dr. Guido Capitani (Villingen)** Oligomeric interfaces in transmembrane proteins: an analysis
14:10-14:45	**Prof. Jaroslav Burda (Prague)** Interaction of metallodrugs with DNA, QM/MM MD study
14:45	**Poster & Lecture awards, Closing**

POSTER SESSION I

Tuesday, March 18th 2014 14:35-15:35

P01 **Muhammad Akram (Innsbruck)**
Molecular Modeling of 11β-hydroxysteroid dehydrogenase type 2 inhibition, glucocorticoid antagonism, and mineralocorticoid agonism for predicting chronic toxic effects of phytochemicals

P02 **Thomas S. Asche (Hannover)**
Inorganic-Organic Hybrid Polymers: A Force Field Modeling Approach

P03 **Akın Azizoğlu (Balikesir)**
Substituent Effects on the Aromaticity of Cyclopropenium Analogues

P04 **Richard Bartelt (Halle)**
MOE interface for multidimensional MOPAC scan calculations using the example of prenylating enzymes

P05 **Thilo Bauer (Erlangen)**
Modeling Charge Transport in SAM-FETs with Quantum Monte Carlo

P06 **Frank Beierlein (Erlangen)**
Ion and pH Effects on Foam Protein Aggregation

P07 **Zlatko Brkljača (Erlangen)**
Determining the stereochemistry and key excitations in the CD spectra of organic molecules by theoretical methods

P08 **Hanno Dietrich (Erlangen)**
Modelling Self-Assembly of Phosphonic Acid on Aluminum Oxide Surfaces

P09 **/**

P10 **Ahmed El Kerdawy (Erlangen)**
Rigid-Body Molecular Alignment Using Quantum-Mechanics-Derived Local Properties

P11 **Roland Frach (Dortmund)**
Solvation effects on chemical shifts by 3D RISM theory

POSTER SESSION I

Tuesday, March 18th 2014 14:35-15:35

P12 **Susan Gruner (Halle)**
Systematic investigation of protein-protein docking servers for auxin response related proteins

P13 **Elke Haensele (Portsmouth)**
Urotensin-Related Peptide (URP) Long-term Molecular-Dynamics Simulation

P14 **Leonhard M. Henkes (Dortmund)**
Thermodynamic and kinetic ion selectivity of phospholamban

P15 **Anselm H. C. Horn (Erlangen)**
On a Potential Sodium Effect in Fibrillar Amyloid-β Oligomers

P16 **Hari Narayana Moorthy (Porto)**
Molecular Modelling Studies on Farnesyltransferase Inhibitors

P17 **Ralf Kling (Erlangen)**
Active-state model of a dopamine D_2 receptor - $G\alpha_i$ complex stabilized by aripiprazole-type partial agonists

P18 **Berin Karaman (Halle)**
Development and validation of MM-(GB)SA models for predicting the biological activity of sirtuin inhibitors

P19 **Teresa Kaserer (Innsbruck)**
In silico predictions of drug-drug interactions caused by CYP1A2, 2C9 and 3A4 inhibition – a comparative study of virtual screening performance

P20 **Patrick Kibies (Dortmund)**
Conformational and tautomer sampling of small molecules in solution with quantum-chemical accuracy

Please remember to remove your posters on tuesday evening!

POSTER SESSION II

Wednesday, March 19th 2014 10:05-11:05

P01 **Anna Kahler (Erlangen)**
Conformational stability and oligomerization properties of the viral GPCRs US27 and US28

P02 **Sebastian Lilienthal (Hannover)**
Understanding adsorption in Zr-organic frameworks:
A computational study

P03 **Johannes Margraf (Erlangen)**
The Electronic Structure of Amorphous and Graphitic Carbon Nanoparticles

P04 **Stefania Monteleone (Innsbruck)**
Ab Initio Modeling of Calcium Channel Voltage-Sensing Domain

P05 **Christof Jäger (Erlangen)**
The hpCADD NDDO-based Polarizable Force Field: Classical Force-Field Potentials and Parameterizatio

P06 **Giulia Pagani (Düsseldorf)**
The HPA-1 polymorphism impacts the platelet-specific integrin αIIbβ3 by a ripple effect

P07 **Soujanya Pasumarthi (Vaddeswaram)**
An inverse docking approach for identifying new potential anticancer Targets

P08 **Achim Sandmann (Erlangen)**
Do we need to analyze μs MD simulations differently?

P09 **Achim Sandmann (Erlangen)**
Conformational variability of the p53 core domain

P10 **Michael Schauperl (Innsbruck)**
Hydration Properties with Polarizable Multipole Force Fields

P11 **Filip Šebesta (Prague)**
Formation of PtII(DACH)Cl2 from PtIV(DACH)Cl4 in the presence of dGMP. DFT study

P12 **/**

POSTER SESSION II

Wednesday, March 19th 2014 10:05-11:05

P13 **Dmitry Sharapa (Erlangen)**
Cubic C8 – An Aromatic Carbon Cluster?

P14 **Eileen Socher (Erlangen)**
H238N Mutant of Hsp47: Molecular Mechanism of Disrupted Collagen Binding

P15 **Joachim D. Stump (Erlangen)**
Unexpected Effect of Somatic Mutations on the Affinity of an Antibody by Altering Its Dynamics

P16 **Andreas Truszkowski (Duisburg)**
Extension of molecular fragment based mesoscopic simulation to the biopolymer realm

P17 **Tanaporn Uengwetwanit (Halle)**
Optimization of post-docking strategies for hit identification of HCV NS5B polymerase inhibitors

P18 **Birgit Waldner (Innsbruck)**
Impact of local dynamics and local interaction potentials on serine protease recognition

P19 **Cem Burak Yıldız (Aksaray)**
Theoretical Study on Silaspiropentanation Reactions of Silacyclopropylidene and Silacyclopropylidenoid

P20 **Dejan Zagorac (Erlangen)**
Overview of modern computational methods in the research of advanced materials from bulk crystals to nanoscale structures

All poster abstracts are available here:
www.mmws2014.mgmsds.de

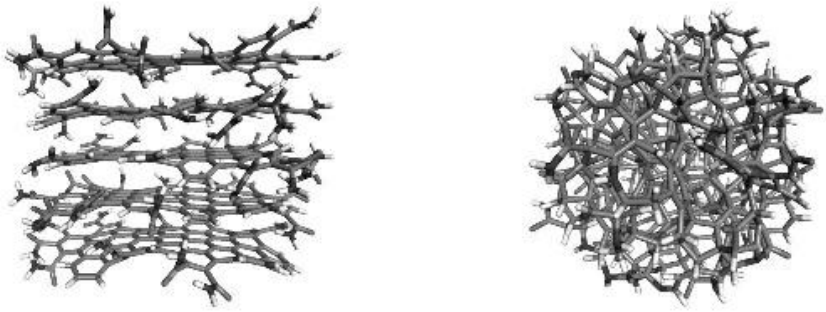
The Electronic Structure of Amorphous and Graphitic Carbon Nanoparticles

Johannes T. Margraf,[1,2] Volker Strauß,[2] Dirk M. Guldi,[2] Timothy Clark[1]

[1]*Computer Chemie Centrum, Nägelsbachstr. 25, 91052 Erlangen*

[2]*Physikalische Chemie I, Egerlandstr. 3, 91058 Erlangen*

Carbon nanodots (CNDs) can easily be synthesized from small molecules and feature interesting properties, most prominently strong, tunable photoluminescence and high water solubility. The structure of these materials is difficult to study experimentally because the particles are usually quite polydisperse. Additionally, CNDs consist exclusively of light elements (C,N,O) with low scattering cross-sections towards electron and X-ray radiation, limiting the use of many important characterization methods (e. g. TEM, XRD).



We have developed two distinct structural models for CNDs. On the one hand, we constructed heavily functionalized graphene/graphite particles. On the other hand, we considered amorphous carbon spheres with relatively low density, which feature a considerable amount of sp^2 atoms. In this case the role of nitrogen impurities was also investigated. To study the geometry and electronic structure of these models (which consist of thousands of atoms), we relied on the massively parallel semi-empirical molecular orbital theory program EMPIRE.[1]

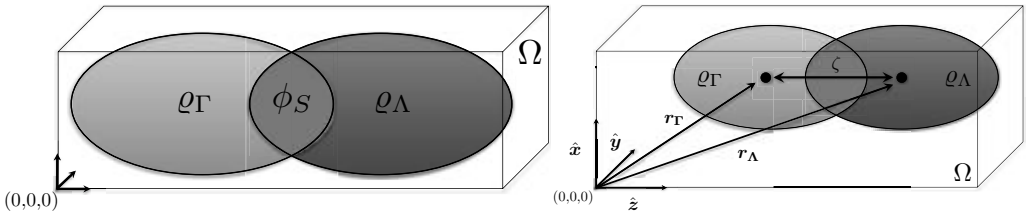
[1] Clark, T.; Hennemann, M. EMPIRE; Friedrich-Alexander- Universität Erlangen-Nürnberg: Erlangen, Germany, 2011.

A quantitative assessment of electronic transitions' charge-transfer character

T. Etienne, X. Assfeld, A. Monari

Laboratoire SRSMC, Théorie-Modélisation-Simulation
Université de Lorraine
Unité de Chimie Physique Théorique et Structurale
Université de Namur

The present communication relates recent studies devoted to a topological descriptor of photoinduced electronic charge density variation, called ϕ_S. This new index consists in a quantity related to detachment and attachment densities overlap, where the detachment and attachment physically represent electronic density depletion and increment induced by light absorption. Complementarily to former approaches based on direct space charge density variation, our new method provides a simple way to evaluate the charge transfer induced by light absorption. This index can be used as a diagnostic test of exchange-correlation functionals. Furthermore, this model can lead to the evaluation of new push-pull dyes charge-transfer ability to assess their potentiality as candidates for dye-sensitized solar cells. After discussing the new ϕ_S descriptor's mathematical foundations from various perspectives (detachment/attachment densities, natural transition orbitals), its application to several types of chromophores will be exposed. Connexions and divergences will finally be drawn with formerly known indices.



[1] T. Etienne, X. Assfeld, A. Monari, *J. Chem. Th. Comp., submitted* .
[2] I. Ciofini, T. Le Bahers, C. Adamo, F. Odobel, D. Jacquemin, *J. Phys. Chem. C.*, **2012**, *116*, 11946-11955. 2012.
[3]M.J.G. Peach, P. Benfield, T. Helgaker, D.J. Tozer, *J. Chem. Phys.,* **2008**, *128*, 2008, 044118-044118-8.

CO_2 absorption in protic ionic liquids

Dzmitry S. Firaha, Barbara Kirchner

Mulliken Center for Theoretical Chemistry,
Rheinishe Friedrich-Wilhelms-Universität Bonn, Beringstr. 6, D-53115 Bonn

The gas absorption and separation processes in ionic liquids (ILs) assume significant importance among the different applications of ILs. For the improvement of these processes the in depth understanding of solvation, thus, solute-solvent interactions is required. Recently the physisorbed CO_2 and its influence on the carbene formation (chemisorption) in 1-ethyl-3-methylimidazolium acetate [1, 2] were studied in our group. So far the characteristics of the CO_2 absorption in protic ionic liquids (PILs) – which can be easily synthesized via neutralization of Brønsted acid and base – remain uncovered from the microscopic point of view. Interestingly, there are many open questions concerning CO_2 absorption in PILs. For example, how do the PILs in principle dissolve and interact with CO_2? Does the PIL structure change when CO_2 enters ? Do CO_2 molecules tend to be apart or aggregate, and if CO_2 clusters are formed, what is the structure of these clusters? To answer these points, we studied the CO_2 absorption by ab initio molecular dynamics simulations at the example of ethylammonium nitrate. Microheterogeneity of the alkyl chains and the extended hydrogen bond network were observed. Thus, the entire structure of the investigated PIL mixed with CO_2 resembles closely the one of the pure liquid. Our data indicates that while CO_2 most likely creates an energy loss due to entering the liquid via the too small voids, this is fully compensated by specific attractive interaction of CO_2 with the cation and anions of ethylammonium nitrate. This result might serve as an explanation for the question why the ionic liquid is not swelling through CO_2 uptake. The CO_2 cluster formation, which shows a structure similar to supercritical CO_2, is determined by the unpolar groups in CO_2 solvation shell.

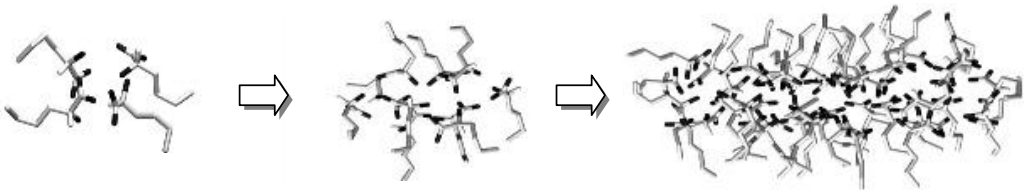
[1] O. Hollóczki, Z. Kelemen, L. Könczöl, D. Szieberth, L. Nyulászi, A. Stark, B. Kirchner, *ChemPhysChem* **2013**, *14*, 315–320.
[2] O. Hollóczki, D. S. Firaha, J. Friedrich, M. Brehm, R. Cybik, M. Wild, A. Stark, B. Kirchner, *J. Phys. Chem. B* **2013**, *117*, 5898–5907.

Nucleation of molecular crystals

Philipp Ectors [1], Jamshed Anwar [2], Dirk Zahn [1]

Chair of Theoretical Chemistry / Computer Chemistry Center

University of Erlangen-Nürnberg[1].
Department of Chemistry, Lancaster University[2]



4 molecules *10 molecules* *50 molecules*

We investigate the early stages of molecular crystal nucleation by means of a combined Monte-Carlo/molecular dynamics simulation approach. Along this line, the time scales for solute migration to the aggregate are efficiently bridged, whilst detailed simulated annealing is applied to aggregate relaxation.

Starting from a dimer, the Kawska-Zahn method allows the investigation of the mechanisms of molecule-by-molecule association, the formation of pre-nucleation clusters, nucleation and aggregate growth [1].

Here, we demonstrate this approach for two molecular species, i.e. D/L - norleucine and benzamide. While the polymorphism of the former has been thoroughly explored by Anwar et al [2], dispersion-corrected density functional calculations are used to rationalize the subtile energy differences in the most important polymorph structures of benzamide.

On the basis of this in-depth understanding we suggest nucleation scenarios as guide to synthesis [3,4,5].

The pictures illustrate the early stages of D/L - norleucine molecule association (left) and the transition (middle) to later stages of aggregate growth with reflect the formation of layered structures (right).

[1] A.Kawska, J.Brickmann, R.Kniep, O.Hochrein, D.Zahn, J. Chem. Phys., **2006**, 124, 24513.
[2] Sigrid C. Tuble, Jamshed Anwar, and Julian D. Gale , J. Am. Chem. Soc. , **2004**, 126, 396 - 405
[3] P. Ectors, D. Zahn, Phys. Chem. Chem. Phys., **2013**, 15, 9219
[4] P. Ectors, D. Ectors, D. Zahn, Mol. Simul., **2013**, DOI**:**10.1080/08927022.2013.794274
[5] Christian Butterhof, Thomas Martin, Phillip Ectors, Dirk Zahn, Paul Niemietz, Jürgen Senker, Christian Näther, Josef Breu; Cryst.Growth Des., **2012**, 12, 5365-5372

Scaffold analysis in Python with RDKit and pandas

Samo Turk[1], Sameh Eid[1], Andrea Volkamer[1], Friedrich Rippmann[2] and Simone Fulle[1]

[1] *BioMed X Innovation Center, Im Neuenheimer Feld 583, 69120 Heidelberg, Germany*

[2] *Merck KGaA, Merck Serono, Global Computational Chemistry, Frankfurter Str. 250, 64293 Darmstadt, Germany*

Dealing with big data analysis can be a significant challenge for a computational chemist. While there are some established off the shelf tools, one often finds them cumbersome and prefers the flexibility provided by programming languages. In this line, Python [1] is one of the most popular programming languages used in science. This is mainly due to its simple but elegant syntax as well as a large number of freely available modules and libraries. Python is getting popular even in the domain of data analysis which was traditionally reserved for R [2].

The most mature data analysis library for Python is pandas [3] and the most mature chemistry toolkit with Python bindings is RDKit [4]. With the help of RDKit, pandas can be chemistry aware, enabling rapid analysis of large amounts of chemical data. In addition, interactive programming environments such as Ipython [5] make chemical data analysis even more approachable.

Here, we will present some basic chemoinformatics operations provided by RDKit and pandas as well as new functions contributed by us to the RDKit community. For example, we will demonstrate how to read in chemical data, calculate descriptors, perform filtering based on these descriptors, and how to visualize these results. In particular, we will demonstrate how our contributions to the RDKit code allow efficient scaffold analysis for a set of compounds.

[1] Python Programming Language – Official Website - http://www.python.org/
[2] The R Project for Statistical Computing - http://www.r-project.org/
[3] Python Data Analysis Library — pandas: Python Data Analysis Library - http://pandas.pydata.org/
[4] RDKit - http://www.rdkit.org/
[5] IPython - http://ipython.org/

Redesigning Drug Design

John Codera

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Drug design lags far behind other engineering disciplines in lacking predictive, quantitative models that allow small-molecule therapeutics to be designed, rather than fortuitously discovered. While many challenges exist to building these models, our laboratory uses cycles of computational predictions coupled to experimental measurements to rapidly generate data that can be used to improve rigorous, quantitative approaches to small molecule design based on alchemical free energy calculations. In this talk, we will describe how this process can be done cheaply and in a fully automated manner by inverting the drug discovery problem, and describe our first few steps toward this goal.

Optimization of post-docking strategies for hit identification of HCV NS5B polymerase inhibitors

Tanaporn Uengwetwanit and Wolfgang Sippl

Department of Pharmaceutical Chemistry, Martin-Luther University Halle-Wittenberg, 06120, Halle (Saale), Germany

NS5B is an RNA-dependent RNA polymerase (RdRp), a key enzyme in HCV replication process, and a well validated drug target[1]. In an effort to establish an efficient for computational screening of HCV polymerase inhibitors, we tried a systematic combination of docking and post-docking strategies. Glide standard precision (SP) docking which allow flexible hydroxyl groups was applied to a set of known inhibitors [2]. We present an evaluation of 3 post-docking strategies including random forest (RF) classification, structural interaction fingerprint (SIFT)[3], and incorporation of docking to dummy binding sites. Random forest, an ensemble leaning method, was trained by 397 known inhibitors and used to build two models. RF model-1 predicted the compounds to bind or unbind and model-2 classified the compounds into potent or weakly actives. Structural interaction fingerprint was used to compare the interaction similarity of a given compound to the known inhibitors. But instead of one to one comparison between two molecules, we derived conserved interaction patterns from 29 crystal structures and used those as references. The last strategy called "two sites docking", compared the docking to a target site with docking to a dummy binding site. Both binding sites show different binding site structures. The compounds which scored well in both binding sites were discarded. This strategy was based on an idea that a good candidate compound should specifically bind only to one target binding site. All procedures were validated by enrichment studies of a collection of 99 known HCV polymerase inhibitors and 1693 decoys. The results show that combining Glide SP with RF models provides a substantially better discrimination than the other methods in case of the validation subset-1. RF model-1 could obtain 18 known inhibitors among the 20 top ranked compounds (about 1% top ranking). However, the RF model has the limitation that it predicts well what has used for training. In the validation subset-2, only 5 known inhibitors were found among the 1% top ranked hits. Thus without prior knowledge of inhibitors, two sites docking should be considered as most suitable strategy. Within all validation sets two sites docking accurately predicts 16 known inhibitors among the 20 top ranked compounds.

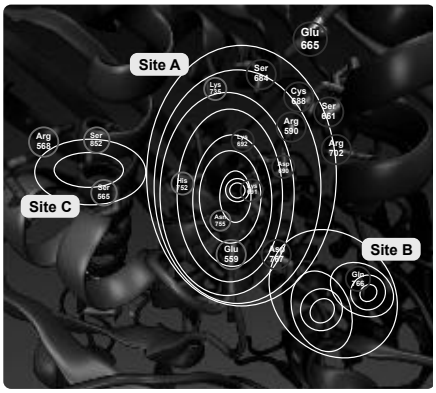
[1] C. M. Lange, C. Sarrazin, S. Zeuzem, *Aliment Pharmacol Ther* **2010**, *32*, 14-28.
[2] R. A. Friesner, J. L. Banks, R. B. Murphy, T. A. Halgren, J. J. Klicic, D. T. Mainz, M. P. Repasky, E. H. Knoll, M. Shelley, J. K. Perry, D. E. Shaw, P. Francis, P. S. Shenkin, *J Med Chem* **2004**, *47*, 1739-1749.
[3] Z. Deng, C. Chuaqui, J. Singh, *J Med Chem* **2004**, *47*, 337-344.

Binding Mode prediction of HMG-CoA Reductase Inhibitors Using Molecular Modelling Tools

N.S. Hari Narayana Moorthy, Nuno N.M.F.S. Cerqueira, Maria J. Ramos, Pedro A. Fernandes

REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, 687, Rua do Campo Alegre, 4169-007 Porto, Portugal.

HMG-CoA reductase (HMG-CoA-R) is currently an important drug target to treat hypercholesterolemia and cardiovascular diseases [1]. In the present study, 320 compounds with HMG-CoA-R inhibitory activity were studied in order to unravel the source of their inhibitory activity. To this end, molecular dynamic simulations and molecular docking studies were conducted to predict the binding pose of the ligands in the active site of HMG-CoA-R. Further studies, such as solvent accessible surface area (SASA) and protein ligand interaction fingerprint (PLIF), were also conducted to understand which amino acid residues are important in the binding process and are important to control the specificity of the active site. The final results allowed us to divide the compounds in different classes based on their bonding pose and biological activities.



The retrived results have shown that the compounds with fused heterocyclic ring structures in the main scaffold of their structure and that mimics the mevalonic acid bind in the same position of the active site as the natural substrate and, interact very closely with the active site residues Ser565, Glu559, Asp609, Lys691, Lys692 and Arg568 [1,2] (Fig1- site A). These compounds are also the ones that show better biological activity. These results have also shown that the compounds that have bulkier and polar groups capable of interacting with the binding site that is normally occupied by the CoA cofactor tend to improve their inhibitory activity (Fig1 - site C). These studies have also revealed that some of the HMG-CoA-R inhibitors interact with some amino acid residues nearby the binding site that are important in the dimerization of HMG-CoA-R enzyme. These studies suggest therefore that some of the these inhibitors can also act as dimerization inhibitors [1].

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An Open Source Prediction Tool for Assessing Endocrine Disruption Potential through Nuclear Receptors Binding

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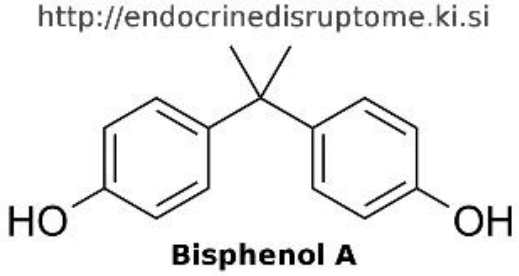

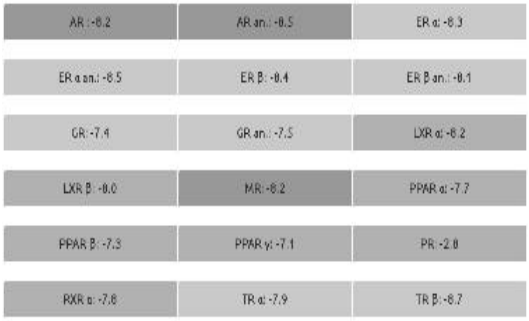

Endocrine disrupting chemicals (EDCs) are substances which can interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormone in both humans and wildlife. A wide range of substances were identified to cause endocrine disruption, ranging from manmade chemicals, including pharmaceuticals, DDT and other pesticides, bisphenol A, and plasticizers such as phthalates, to natural chemicals for instance phytoestrogens [1]. These EDCs can be serious health threat by leading and/or contributing to major diseases [2]. Therefore identification and safety assessment of EDCs is at most utter importance [3].

Traditionally QSAR was used for prediction of endocrine disrupting potential of chemicals. Although QSAR can be very accurate it has its limitations especially because it is mostly limited to structurally related compounds [4]. Our aim was to develop a method that would work on any type of chemical and that would be well validated. We chose 14 nuclear receptors and more than 100 crystal structures of those receptors. Additionally we selected up to 600 active compounds for each receptor and generated up to 30,000 decoys (compounds assumed to be inactive). We used all this data to check the performance of all the crystal structures. The results enabled us to finally select 1 or 2 structures per receptor with the best results.

All data was then integrated in DoTS (Docking interface for Target Systems) which is an open source web platform that enables docking of chemicals to multiple structures at once. DoTS with integrated best performing crystal structures of nuclear receptors forms Endocrine Disruptome.

DoTS source code is available on GitHub (https://github.com/katrakolsek/DoTS) and Endocrine Disruptome can be accessed via http://endocrinedisruptome.ki.si

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Pharmacophore-based discovery of novel inhibitors of the innovative therapeutic target soluble epoxide hydrolase (sEH)

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As a key enzyme within the arachidonic acid cascade, the soluble epoxide hydrolase (sEH) plays an important role in the regulation of inflammation. While the cyclooxygenase (COX) and lipoxygenase (LO) enzymes produce largely pro-inflammatory metabolites, the cytochrome P450 epoxygenases metabolize arachidonic acid into anti-inflammatory epoxyeicosatrienoic acids (EETs). These endogenous compounds are rapidly oxidized to the corresponding dihydroxyeicosatrienoic acids (DHETs) by sEH. Inhibitors of sEH block this degradation and therefore stabilize EET levels, which leads to an enhancement or extension of the anti-inflammatory effect. Hence, there is an increasing interest in this potential therapeutic strategy for treating inflammatory disorders. [1-3]

This study aimed at the identification of novel potent sEH inhibitors. Therefore, several structure- as well as ligand-based pharmacophore models for sEH inhibitors were developed and theoretically validated using data from literature. The best eight models were used as a search query to virtually screen the chemical database supplied from the Specs. For each model, six virtual hits showing high fit values were selected for biological investigation in a fluorescence-based enzyme activity assay. At least one of the six virtual hits, respectively, displayed a sEH remaining activity of less than 35% of control at a concentration of 10 µM. In total, out of 48 compounds, eight compounds of different chemical scaffolds showed a sEH remaining activity of less than 60% of control at a concentration of 0.1 µM and IC_{50} values in the low nanomolar range. The most active compound exhibited an IC_{50} of 5.0 nM.

Within this study, pharmacophore modeling and virtual screening led to the identification of novel potent inhibitors of sEH, a promising anti-inflammatory target.

Acknowledgements: This work was supported by the Austrian Science Fund (FWF; NFN-S10703 and S10711) and the Tyrolean Science Fund (TWF).

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Development and validation of MM-(GB)SA models for predicting the biological activity of sirtuin inhibitors

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Silent information regulator 2 (Sir2) proteins, also named sirtuins (SIRTs), are NAD+ dependent histone deacetylases distributed in lifeforms ranging from prokaryotes to eukaryotic organisms. To date seven sirtuin subtypes have been identified in humans; SIRT1-7 that share a highly conserved catalytic NAD+/acetyl-lysine binding site. Human sirtuins SIRT1-3 represent interesting targets related to the treatment of age related diseases, neurological disorders (like Parkinson`s and Alzheimer`s diseases), metabolic syndromes (such as diabetes and obesity), viral diseases and cancer [1, 2]. Most of the sirtuin modulators that have been identified so far show limited potency and/or isoform selectivity. Therefore, the development of potent and specific inhibitors of sirtuins might help to evaluate their pharmacological potential for several diseases and exploiting their functions in cellular processes.
In order to rapidly screen large compound databases, docking-based virtual screening (VS) approaches have been used to predict the binding strength of ligands. However, current scoring functions show a poor correlation with biological data and more rigorous methods are in need. In this study, we present an MM-(GB)SA approach that can be used as an effective post-docking filter tool to enrich VS results and prioritize hits for further biological testing.

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First-principles molecular structure search with a genetic algorithm

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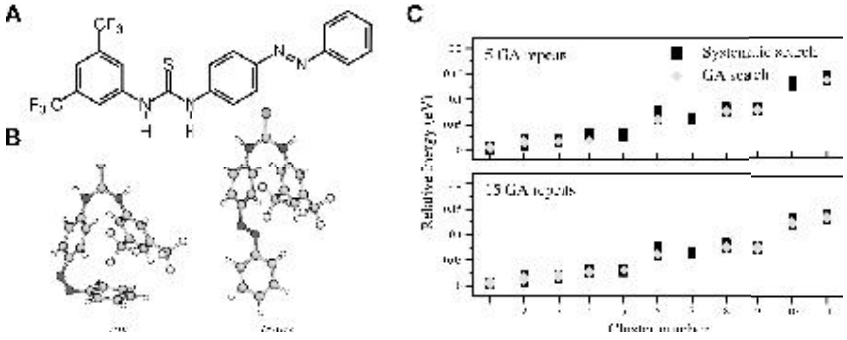
We present a genetic algorithm (GA) based framework for structural searches of complex molecules based on empirical or first-principles (density-functional theory, DFT) energy functions. The aim is not just to find the single global minimum structure, but also to identify all conformers that appear in the low-energy conformational hierarchy and thus could be experimentally relevant. The use of DFT gives access to rather accurate energy functions and avoids the problem of parameterization for specific classes of chemical compounds.

In our GA search, the geometry of a structure is encoded in a vector of torsional degrees of freedom (TDOF). The initial population of *N* individuals is randomly generated and evaluated by local geometry optimization. Two individuals are selected; the selection probability is a function of the energy. Next, genetic operations are applied: (i) crossing over exchanges parts of the encoding vectors and (ii) mutations randomly assign new values to selected TDOFs. The resulting candidate structures are again evaluated by local relaxation and eventually replace individuals of the previous generation with a higher energy. The algorithm proceeds with a new selection round until a predefined number of iterations or a convergence criterion is met. Generated geometries are first checked for steric clashes and for uniqueness (that is if they were computed already before) based on the root mean square deviation (rmsd) of Cartesian coordinates. This greatly reduces the number of unproductive or redundant calculations, which is especially important when using a first principles energy function.

We demonstrate the principle for an azobenzene-based molecule (the chemical structure is shown in Figure A), finding the conformational energy hierarchy for the *cis* and for the *trans* configurations (the global minima are depicted in Figure B). In order to verify if the conformational energy hierarchy from a systematic search can be reproduced by a GA search, the structures yielded by the systematic search were clustered into 11 clusters and the structures from GA repeats were sorted into these clusters. The accuracy of such a GA prediction is critically linked to the search settings, for example, the number of repeats (illustrated in Figure C). While the global optimum is found very reliably with only a few repeats, the reproduction of the hierarchy is more demanding. Similar testing was performed for seven amino acid dipeptides (Ala, Gly, Val, Leu, Ile, Phe, Trp).



Post-processing of the data, for example the evaluation of the geometrical similarity of the structures and taking into account their energetic relation, allows for visualization of the topology of the potential energy landscape in form of a graph. Such information can be further utilized to identify which pairs of states are likely to be connected by a low-energy barrier. We will use the described strategy to predict functional molecules (by adding a library of side groups) that are tuned for a specific use, e.g., as switchable catalysts of a target chemical reaction.

A marginal stability is required for the guanine-sensing riboswitch to function

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Riboswitches are small genetic regulatory RNA elements that control bacterial gene expression on the transcriptional or translational level upon binding of ligand molecules. The ligand binds to the riboswitch aptamer domain, inducing a conformational change in the downstream expression platform. In transcriptionally acting riboswitches, this conformational change of the expression platform leads to the formation or disintegration of an intrinsic transcription terminator loop, thus switching gene expression off or on. Since transcriptional gene regulation by riboswitches has to happen in a narrow time window during the transcription process, detailed knowledge about the unbound state of the riboswitch is crucial to understand the overall process underlying the regulation decision by the riboswitch.

While insights into the bound state of purine-sensing riboswitches on the atomic level are available from crystal structures and other experimental investigations, such atomic level details about the unbound state and its dynamics are still scarce.

We investigate the unbound state of the guanine-sensing riboswitch aptamer domain (Gsw) and a mutant using molecular dynamics (MD) simulations in explicit solvent. In all, we simulated six variants of the system with three replications each, resulting in a total simulation time of more than 10 μs. By probing the system with respect to the strength of tertiary loop-loop interactions or the presence/absence of Mg^{2+}, we gain detailed insights even at simulations times smaller than the anticipated switching time. In particular, we observe a dynamic coupling between the loop region of the Gsw and its ligand binding site located ~25 Å away. Furthermore, Mg^{2+} exerts a stabilizing effect that differently fine-tunes the structural stability of wildtype and mutant. These results suggest that the functional stability of the aptamer domain is highly sensitive to subtle changes in the structure and its environment, and that information on the ligand is transmitted to the expression platform by complex entropic control. These findings are important for understanding how Gsw functions at a molecular level.

Explaining protein-protein interfaces in protease recognition with local dynamics and local interaction potentials

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Proteases are enzymes that catalyze the cleavage of peptide bonds and are important in numerous fundamental cellular processes, ranging from food digestion over blood coagulation to apoptosis. Proteases also account for 1-5% of the genome of infectious organisms such as bacteria, parasites and viruses [1].

While proteases involved in cellular signaling pathways such as the blood coagulation pathway or the apoptosis pathway show high specificity, proteases involved in processes such as the digestion of food proteins show rather low specificity. The specificity of a series of proteases has recently been quantified by Fuchs et al. through calculation of the so-called cleavage entropy as a sub-pocket-wise and overall specificity score [2] based on cleavage data from the MEROPS database [3].

To understand the mechanism of protease recognition, we will present a quantitative correlation between the local dynamics at the binding site of a series of homologous serine proteases with Trypsin-like fold obtained from molecular dynamics simulations and the specificity of the investigated proteases. In addition, we will present GRID [4] analyses for molecular dynamics trajectory snapshots to give a view of local interaction potentials at different conformational states of the proteases using selected probes. Through combination of thermodynamic data from the GRID analyses with the flexibility data obtained from molecular dynamics simulations, we want to give more insight into the interactions at protein-protein interfaces in protease recognition and discuss the contributions of enthalpic and entropic factors to protease substrate recognition.

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Speed of Force Fields: Kinetic Comparison of Force Fields in Biological Systems

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The possibility to explore protein structures and dynamics via Molecular Dynamics (MD) simulations depends on how well the MD force fields capture the true energy landscape of the system under study. Continuous effort in the development of MD force fields is leading to more reliable descriptions of structural and conformational properties of biomolecular systems. In recent years, MD has increasingly been used to infer also kinetic properties of biological systems. One way of achieving this is by means of Markov State Models (MSM), which allows to identify the slowest kinetic processes and the associated time scales. Especially as force fields are usually parametrized only with respect to structural and equilibrium properties, a systematic characterization of force fields respect to kinetic properties has been carried out.

In this study, we performed extensive simulations of a small subset of amino acids and short peptides with four of the most commonly used force fields (AMBER ff99SB-ILDN, AMBER ff03, OPLS-AA and CHARMM27). Our results, in the MSM framework, highlight a force field dependence on the slowest implied timescales, which can vary up to an order of magnitude, even in the simple case of dipeptides; incongruity is also present in the identification of the slowest kinetic processes, especially in the case of small, very flexible, peptides . We suggest a necessity for the development of force fields that are also parametrized with respect to kinetic properties.

DASH: Analysis of microsecond-scale molecular-dynamics trajectories

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Natural time-scales for conformational changes may last milliseconds to seconds, *e.g.* protein-folding. Although current molecular-dynamics simulations (MD) typically cover time scales of 10 to 100 nanoseconds, the computational power has become readily available to run simulations on a microsecond scale.
However, such long simulations create the technical problem of how to analyse the increased volume of output within a reasonable time without being forced to reduce the number of considered data points drastically. This is where common clustering methods reach their limits.
DASH (Dynamic Analysis by Salt and Hudson) [1] provides an alternative solution by using a time series of torsion angles instead of similarity matrices of Cartesian coordinates (clustering) to find representative conformations (states). Time-series analysis is very fast, making ***DASH*** capable of analysing considerable large datasets.
The principles of ***DASH*** will be explained and ***AmberDASH***, an interface for the user-friendly application of ***DASH*** to ***AMBER*** trajectories, will be introduced.
The performance of ***DASH*** and the consistency of its results will be demonstrated using a 5 microsecond MD trajectory of 8Arg-Vasopressin as an example.

DASH 1.0	Program for extracting states from molecular-dynamics simulations; distributed under the terms of the GNU General Public License; download via www.port.ac.uk/research/cmd/software
AmberDASH	*DASH* interface for *AMBER* trajectories (unpublished); currently provided via email (please contact Dr David Whitley david.whitley@port.ac.uk)

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Modeling and Molecular Dynamic Simulations of Calcium Channel Voltage Sensor

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Voltage-gated calcium channels are involved in several diseases, but the investigation of their mechanisms needs an atomic-detailed study of the protein. Mutations in the pore forming α_1 subunit of $Ca_v1.3$ isoform have recently been shown to drive excess aldosterone secretion from aldosterone producing adenomas [1]. Since crystal structures of α_1 subunit are not yet available, we used molecular modeling to predict potential functional changes of one of the mutations in the voltage sensors.
Firstly, homology modeling of the activated state has been performed starting from the X-ray structure of a sodium channel as template [2], only to predict the transmembrane segments because of higher sequence similarity. At a later step, we used the ab initio Rosetta method to model intra- and extracellular loops, without any constraints [3]. The resting state has been modeled starting from the previous model: indeed, since there are no crystal structures for resting voltage sensors of ion channels, we edited the sequence alignment in order to get different matches of key charged residues in the voltage sensor.
Afterwards, models have been minimized in a periodic box including lipids, water molecules and ions, and through molecular dynamic simulations we investigated the most important interactions among charged residues in the resting and activated states.
Moreover, we analyzed the diffusion of water molecules in the voltage sensor in native and mutant proteins: in particular, the mutation of one arginine residue to histidine (R990H) resulted in the formation of a wire of water molecules in the resting state, that was not present in the wild-type protein. This might involve the development of omega-currents in the voltage sensor, that often cause ion channel related diseases [4].

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Self-Consistent Field Convergence for Proteins: A Comparison of Full and Localized-Molecular-Orbital Schemes

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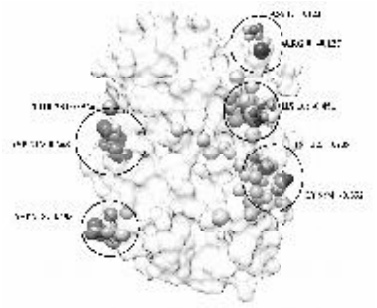
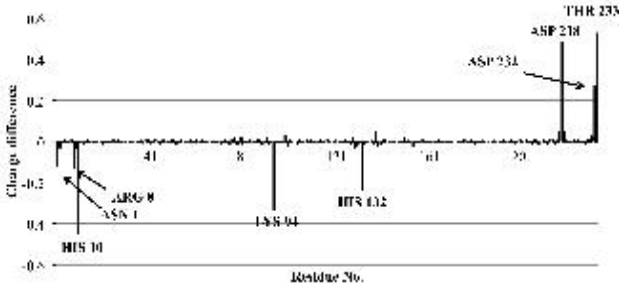
The computational description of systems with tens of thousands of atoms such as proteins is still a molecular mechanics' domain. However, method and hardware developments are gradually leading to a paradigm change. Nowadays, semiempirical wavefunction based MNDO-like [1] NDDO (Neglect of Diatomic Differential Overlap) self-consistent field (SCF) calculations are also applied routinely to larger systems. Besides linear-scaling methods such as divide and conquer (D&C) [2] or localized-molecular-orbital (LMO) [3] techniques, conventional full SCF calculations based on a massively parallel code (EMPIRE [4]) now allow very large systems to be treated without local approximations.

During the development of the massively parallel EMPIRE code, [4] it became evident that SCF convergence is very slow for gas-phase calculations on zwitterionic (i.e. almost all) proteins using a full SCF routine, whereas such calculations converge very effectively using the LMO-SCF technique implemented in MOPAC (MOZYME) [5]. Comparative calculations with both techniques showed that the very slow inductive charge-transfer process that made the conventional SCF calculations so slow to converge is prevented in the LMO-SCF scheme. [6] Therefore, the LMO procedure can lead to artificially over-polarized wavefunctions in gas-phase calculations. For a better understanding of this phenomenon, example molecules have been constructed to demonstrate this behavior.





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An integral equation theory for ligand design

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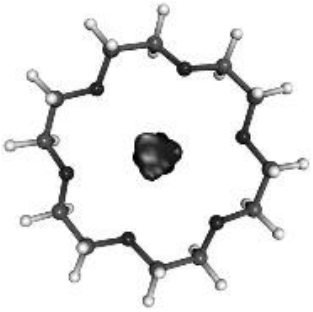
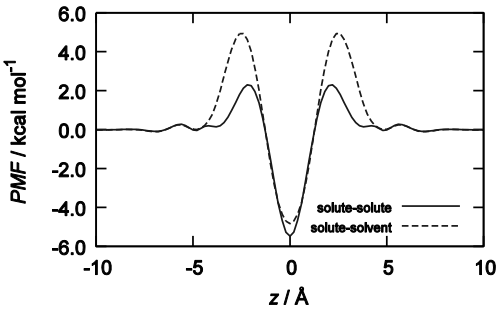
Refining a ligand from an initial hit to a lead molecule is an arduous procedure. Therefore many different methods, experimental as well as computational, were developed to cope with this problem. The computational methods can be divided into classes which differ in their theoretical level, applicable scope, computational demand, and accuracy. Accuracy and computational speed typically diverge for common theoretical modeling approaches. For most rapid virtual high-throughput screening tasks accuracy is gained for structural binding pose predictions only while affinities cannot be determined sufficiently. The most expensive methods, explicit molecular dynamics free energy calculations can yield high affinity accuracy though at the prize of tremendous effort.

As an alternative, integral equation theories that are based on classical density functional theory have the potential to combine computational efficiency with high accuracy [1]. Here we particularly focus on the 3D reference interaction site model (3D RISM) that provides in its basic form solvent site distribution functions around arbitrarily shaped solutes. These equations can be transformed to yield the set of solute-solute pair molecular distribution functions [2] in infinite dilution which represents the proper thermodynamic framework for protein-ligand affinity studies. In particular, the solute-solute equations provide direct, rapid access to the potential of mean force (PMF) between ligands (or fragments and single sites thereof) and a protein host, from which the free energy of binding can be calculated along with maps of potential ligand atom pathways into the binding site.





We describe the mathematical details of the methodology and present several illustrative benchmark applications to host-guest systems. A special benefit of the approach is related to the possibility to compute free energy derivatives with respect to interaction parameters of putative ligand sites [3]. This feature is highly relevant for a classical *computer aided design* process since it allows to rationally modulate chemical properties with the goal to optimize binding affinity, giving rise to an alternative way to score binding poses. This physically appealing characteristic can be efficiently utilized since the methodology is inherently parallel and allows for rapid interactive refinement.

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GPCR structures in drug design: a case study on the residence time of antimuscarinic drugs

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G-protein coupled receptors (GPCRs) are the largest superfamily of receptors and thus one of the most prominent classes of targets for drug discovery. In this talk basic current knowledge about GPCR biology, GPCR signalling and GPCR structure will be presented. In addition to this the use of GPCR structures and homology models will be discussed in the context of drug design. As specific example for the use of GPCR structures to gain deeper understanding of drug-receptor interactions, the interaction of the marketed drug tiotropium with the muscarinic receptor M3 is investigated. Antagonizing the human M3 muscarinic receptor (hM3R) over a long time is a key feature of modern bronchodilating COPD drugs aiming at symptom relief. The long duration of action of the antimuscarinic drug tiotropium and its kinetic subtype selectivity over hM2R are investigated by kinetic mapping of the binding site and the exit channel of hM3R. Hence, dissociation experiments have been performed with a set of molecular matched pairs of tiotropium on a large variety of mutated variants of hM3R. The exceedingly long half-life of tiotropium (of more than 24 h) is attributed to interactions in the binding site; particularly a highly directed interaction of the ligands' hydroxy group with an asparagine (N508) prevents rapid dissociation via a snap-lock mechanism. The kinetic selectivity over hM2R, however, is caused by differences in the electrostatics and in the flexibility of the extracellular vestibule. All these insights are gained from extensive molecular dynamics (MD) simulations (several microseconds) to support experimental results. Simulations are done for wild type hM3R, apo hM3R and for various mutated variants of hM3R and analyses are based on differences in spatial occupancy of the respective amino acids in different MD runs.

Improving SemiEmpirical (NDDO) methods for Born-Oppenheimer Molecular Dynamics

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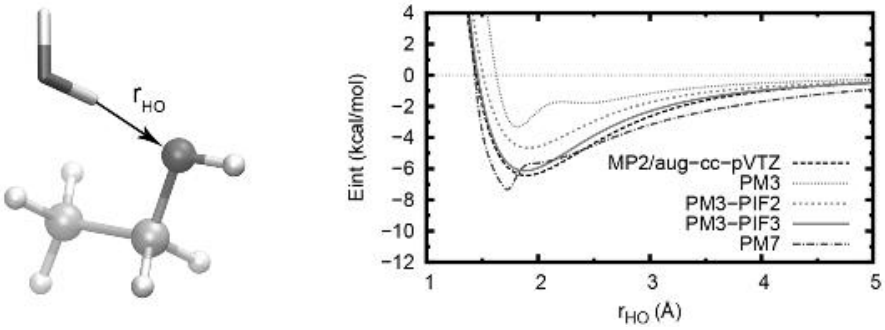
Modeling biomolecular systems by explicitly taking into account the quantum mechanical behavior of the electrons represents one of the greatest challenges for theoretical chemistry studies. Although outstanding progresses have been made in the past decades in performing molecular dynamics (MD) simulations with density functional theory based methods, long time scales and/or systems containing a large number of atoms still demand very high computational costs. A reasonable compromise is represented by the use of a lower level of quantum chemistry to model the electronic Hamiltonian. In particular, semiempirical (SE) methods based on the NDDO (Neglect of Diatomic Differential Overlap) approximation become appealing, since they can be reparametrized and improved.

We recently developed a new scheme allowing us to perform reasonably long MD simulations (up to nanosecond on commodity computer) of large systems (500-1000 atoms with periodic boundary conditions) with a full quantum description of the electrons at a SE level of theory, the so called SEBOMD methodology (SemiEmpirical Born-Oppenheimer Molecular Dynamics).[1] This technique has already been successfully applied to simulate liquid water [1] and N-methyl acetamide [2] in aqueous solution and aims at describing the time dependent behavior of proteins in water including key quantum effects (bond making/breaking, solvent induced polarization and IR shifts, charge transfer ...).

The major bottleneck for a more extensive use of SE methods for condensed phase studies is related to the fact that they were not originally developed to model intermolecular interactions. Some improvements were proposed in the past years for water and small hydrated systems (PM3-PIF2).[3] However, our recent work has shown that none of the SE methods in the literature is reliable to predict the properties of hydrophobic groups in aqueous solution. We have thus developed a new 'force field like' SE approach (PM3-PIF3), in which atom types are taken into account to reproduce high level *ab initio* interaction energy surfaces.[4] Here we shall discuss this methodology and present its application to a few model systems (from simple 1:1 solute-water complexes to biomolecules in aqueous solutions).



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Conformation-related tautomeric shift in 5-formylcytosine

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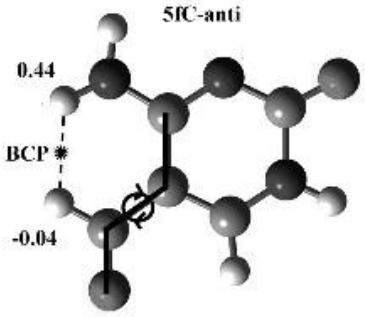
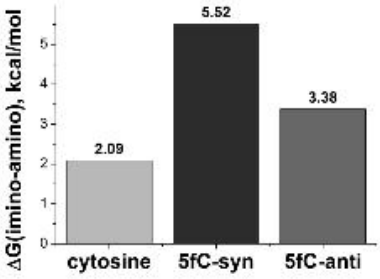
5-formylcytosine (5fC) was found both in DNA and tRNA. Its appearance in DNA corresponds to reactive oxygen species oxidation of 5-methylcytosin (5mC) as well as to its active demethylation by TET proteins. While function (if any) of 5fC in genome remains unclear, its presence in wobble (first) position of mitochondrial $tRNA^{Met}$ anticodon is necessary to decode both AUG and AUA codons as Met and hence to form 5fC·A mispairs[1]. Moreover, there are evidences of its higher mutagenicity and shifted pairing specificity towards adenine at DNA replication[2].

It is known that imino tautomer of cytosine has similar to thymine and uracil pattern of hydrogen bond donor and acceptor groups and can form a Watson-Crick-like basepair with adenine. It was already proposed a role of 5-formyl substituent in shifting of amino-imino equilibrium towards imino form as possible explanation of 5fC pairing properties. There is still no evidence of this hypothesis but there are also any detailed studies of influence of formyl group rotation on amino/imino relative stability in 5fC.

The presence of two conformations related to formyl group rotation was already described by QM methods[3]. For the first time we showed a significant (more than 2 kcal/mol) rise in imino form relative stability in *anti* conformer with respect to *syn* conformer (see figures). We used MP2/cc-pVTZ//B3LYP/6-311++g(d,p) level of theory.





One can see that 5fC-*anti* imino tautomer relative stability doesn't even reach the level of unmodified cytosine, but this effect need to be considered in further studies.
Although the presence of NH--O intramolecular hydrogen bond in *syn* conformer was already detected both theoretically and experimentally, for the first time we showed and verified by means of QTAIM and NBO criteria the presence of dihydrogen bond in *anti* conformer (there are an atomic charges obtained by CHelpG scheme near hydrogen atoms on the figure). We also conducted a detailed investigation of hydrogen bonds characteristics variations along formyl group rotation.

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Parameterization of the hpCADD NDDO-based Polarizable Force Field: The NDDO Hamiltonian

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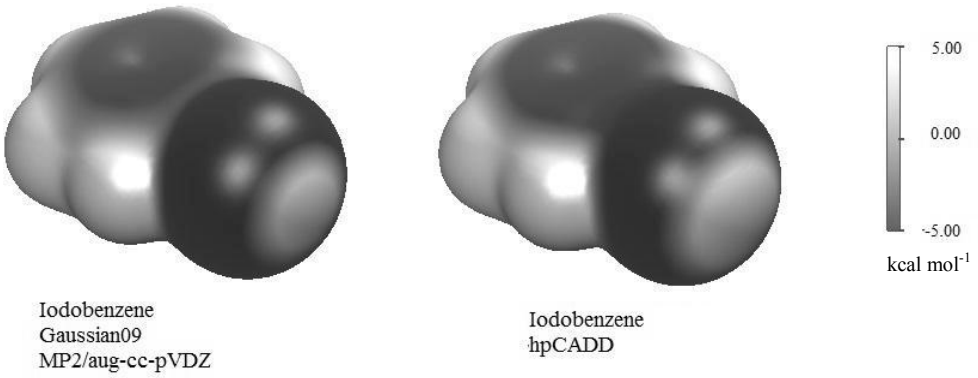
In Computer-Aided-Drug-Design (CADD), the electrostatic interactions contribute significantly to the interaction between the drug-molecule and the target. Further, it is a crucial term for calculating the electrostatic contribution to the solvation energy. In spite of this, conventional Force Fields use the obsolete physical concept of atom-centred point-monopoles and thus, are not able to represent the molecular electrostatic potential (MEP) accurately. They are especially in error for atoms that have positively and negatively charged areas on their surface, such as most halogens [1]. A far better way to describe the MEP is to use atom-centred multipoles derived from semiempirical MO-theory [2,3].

For the parameterization of the polarizable hpCADD Force Field, the two techniques are combined to obtain the MEP from the NDDO wavefunction and structures and energies from a combination of the NDDO-electrostatics with classical force-field potentials. Additionally, distinguishing between different atom types for some elements allows the electronic properties to be reproduced more accurately. This is important for reproducing phenomena such as halogen bonding [4].



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Theoretical characterization and synthesis of gelatin based magnetic hydrogels

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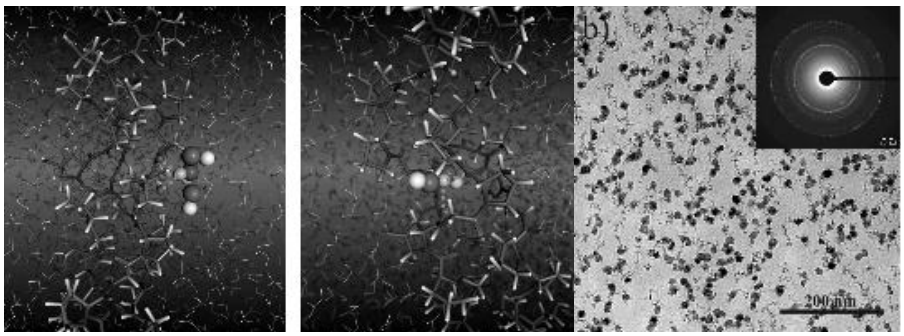
Figure 1: (left) Representative structure for $FeIII(OH)_3$ coordination by collagen. Note that three carbonyl/hydroxyl groups are providing O··Fe salt brigdes via one short (2.3 Å) and two weaker (2.6Å) contacts. (middle) $FeII(OH)_2$ cluster coordination by collagen leading to distorted/incomplete octahedral coordination of FeII (the number of coordinating water molecules from the solvent varies from 0 to 2). Atom colors: Fe (yellow), O (red / green for solvent), H (white), N(blue) and C(grey). (right) TEM image of ultramicro-cuts of an embedded ferrogel at 10 wt% gelatin concentration after 6 reaction cycles (RC) at different magnifications.



We report an easy synthesis of ferrogels based on magnetite synthesis inside a thermoreversible gelatin gel matrix. The structure of the gelatin gel and the magnetite nanoparticles are characterized by X-ray diffraction, electron microscopy and molecular simulations. The simulation studies show the attractive interaction between the gelatin / collagen triple helix and the Fe^{2+} / Fe^{3+} ions and also reveal that collagen is a magnetite nucleator. We demonstrate the response and deformation of the gel in a magnetic field, which suggests that our gels may find applications as biocompatible actuators or switches.

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Large Scale Free Energy Calculations on Congeneric Ligand Series – Applying FEP in Practical Drug Design

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The holy grail of computational structure based ligand design has long been the accurate prediction of binding free energies for novel compounds. Molecular Dynamics based free energy calculations (FEC) have been proposed as one of the most suitable methods to reach this goal, which would significantly impact the modern drug design process. However, despite many successful studies, FEC have for more than 20 years failed to fulfill this promise. Possible reasons for this include force field deficiencies, insufficient sampling and difficulties in assessing the quality of simulation results. One of the main obstacles in addressing these issues has been the lack of large scale validation studies on diverse series of ligands, due to the lack of computational resources and the time consuming process of simulation setup and analysis.
Here, we will present results from FEC conducted on several protein-ligand systems of pharmaceutical interest. Covering more than 10 targets and more than 200 compounds, the results offer more than an order of magnitude more data than typical FEC studies and allow statistically valid conclusion about their efficacy. We show that relative binding free energies can be calculated with good accuracy in most cases, typically with R^2 values in the range of 0.5-0.8 and mean unsigned errors (MUE) of less than 1 kcal/mol on average when comparing to experimental data. We show that FEC consistently outperform other binding energy estimation methods such as Docking and MMGBSA. Statistical error estimates from individual calculations are much smaller than observed deviations from experimental results, but improved error estimates can be obtained from constructing redundant graphs of ligand transformations.

Sensing Organic Molecules by Charge Transfer through Aptamer-Target Complexes: Theory and Simulation

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Aptamers, i.e., short sequences of RNA and single-stranded DNA, are capable of specificilly binding objects ranging from small molecules over proteins to entire cells. Here, we focus on the structure, stability, dynamics, and electronic properties of oligonucleotides that interact with aromatic or heterocyclic targets. Large-scale molecular dynamics simulations indicate that aromatic rings such as dyes, metabolites, or alkaloides form stable adducts with their oligonucleotide host molecules at least on the simulation time scale. From molecular dynamics snapshots, the energy parameters relevant to Marcus' theory of charge transfer are computed using a modified Su-Schrieffer-Heeger Hamiltonian, permitting an estimate of the charge transfer rates [1]. In many cases, aptamer binding seriously influences the charge transfer kinetics and the charge carrier mobility within the complex, with conductivities up to the nanoampere range for a single complex. We discuss the conductivity properties with reference to potential applications as biosensors [2].

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Oligomeric interfaces in transmembrane proteins: an analysis

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Thanks to the increasing amount of transmembrane protein (TM) structures being solved, it is now possible to carry out extensive studies of oligomeric interfaces in the transmembrane region. We have compiled the first fully comprehensive dataset of validated transmembrane protein interfaces (TMPBio) in order to study their features and assess what differentiates them from their soluble counterparts [1]. The general features of interfaces in the TMPBio set do not differ much from those of soluble proteins: they are large, tightly packed and possess many interface core residues. Notably, membrane lipids were not found to significantly mediate interfaces in TMPBio. We also used the dataset to validate the performance of our Evolutionary Protein Protein Interface Classifier (www.eppic-web.org) [2], developed on soluble protein data, on membrane proteins and found it to be about 80%. Although no G protein-coupled receptor (GPCR) was included in the validated set, we analyzed the crystallographic dimerization interfaces proposed in the literature. We found that the putative dimer interfaces proposed for class A GPCRs do not show the usual patterns of stable biological interfaces, neither in terms of evolution nor of packing, thus they likely correspond to crystal interfaces. We cannot however rule out the possibility that they constitute transient or weak interfaces. In contrast we do observe a clear biological interface signature for the proposed dimer of the class F human Smoothened receptor [3].

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Interaction of metallodrugs with DNA, QM/MM MD study

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Biologically relevant interactions of piano-stool ruthenium(II) complexes with ds-DNA are studied in this paper by hybrid QM/MM computational technique. The whole reaction mechanism is divided into three phases: i) hydration of the $[Ru^{II}(\eta^6\text{-benzene})(en)Cl]^+$ complex, followed by ii) monoadduct formation between the resulting aqua-Ru(II) complex and N7 position of one of the guanines in the ds-DNA oligomer model and the final phase – iii) formation of the intra-strand Ru(II) bridge (cross-link) between two adjacent guanines. Free energy profiles of all the reactions are explored by QM/MM MD umbrella sampling approach where the Ru(II) complex and two guanines represent a quantum kernel, which is described by DFT methods. The combined QM/MM scheme is realized by our own software (QMS v. 1.4), which was developed to couple several quantum chemical programs (in this study Gaussian 09) and Amber 11 program. Calculated free energy barriers of the both ruthenium hydration and Ru(II)-N7(G) DNA binding process are in good agreement with experimentally measured rate constants. Then this method was used to study a possibility of cross-link formation. One feasible pathway leading to Ru(II) guanine-guanine cross-link with synchronous releasing of benzene ligand is predicted. The cross-linking is exergonic process with energy barrier lower than for monoadduct reaction of Ru(II) complex with ds-DNA.

Molecular Modeling of 11β-hydroxysteroid dehydrogenase type 2 inhibition, glucocorticoid antagonism, and mineralocorticoid agonism for predicting chronic toxic effects of phytochemicals

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A large number of people around the globe is using plant constituents as food and/or as medicine in their daily life [1, 2]. Most of them are unaware of potentially harmful effects of used plant constituents. 11β-hydroxysteroid dehydrogenase is the enzyme which catalyzes the interconversion of cortisone and cortisol in humans [3]. Our objective is to predict the chronic immunologic and cardiovascular toxicity of commonly used plant constituents, inhibiting11β-hydroxysteroid dehydrogenase type 2, mineralocorticoid activation and glucocorticoid blockade. Pharmacophore based virtual screening will be used for selection of putatively active compounds. Widely used phytochemicals will be evaluated by *in vitro* methods after filtering by *in silico* models. Therefore we propose to identify the toxicological effects of commonly consumed plant constituents.

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Acknowledgements

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Inorganic-Organic Hybrid Polymers: A Force Field Modeling Approach

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Inorganic-Organic Hybrid Polymers like ORMOCER®s offer a wide range of tunable properties. This makes them suitable for many applications, from simple coatings to complex optical or biomedical demands. [1] ORMOCER®s are synthesized in a two-step synthesis (Fig. 1), the first step being a (poly)condensation of silanols or alkoxysilanes – the precursors – resulting in the so-called resin, an organically modified inorganic-organic network with a cross-linked $[Si\text{-}O]_n$ backbone. The resin may already contain a large number of different species, leading to a rather complex system. In the second step, a polymerization is initiated either thermally or photochemically via UV irradiation or two-photon absorption.

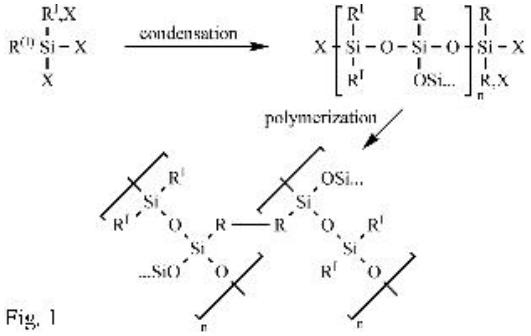

Fig. 1

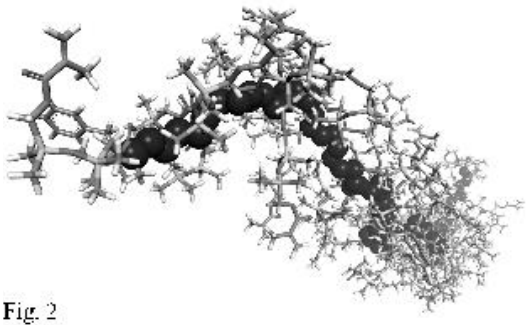

Fig. 2

The macroscopic properties of these materials have been determined in detail, nevertheless the structure of these materials on an atomistic scale is still unknown. Therefore, the application of modeling techniques to gain more insight into the molecular structures seems a suitable approach. Due to the complexity of the investigated materials, only force field methods are resonable for this modeling study. The COMPASS force field was chosen because its applicability for ORMOCER®s was already proven in previous studies. [2]

Here, we present the model system ORMOCER®-DIM01 that forms only two different species in the resin. The ratio of these species was determined by ^{29}Si-NMR spectroscopy. The degree of conversion after the polymerization reaction was obtained by RAMAN spectroscopy. Our models represent all three stages of the material, namely the precursor, the resin and the polymer.

Precursor and resin models are used for validation purposes, mainly to define the appropriate size of the models and the parameters for Molecular Dynamics. These simulations are performed to describe macroscopic properties at room temperature, e.g. the density as a first benchmark for the practicability of our models.

The polymer models consist of organic polymer chains (Fig. 2, backbone shown as balls) with a length of 10 – 100 repeat units, giving simulation cells with up to 4600 atoms. They contain either individual or cross-linked chains, depending on thermoplastic or thermosetting behavior, respectively. The structure of all models is entirely amorphous, which is in agreement with X-ray diffraction data.

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Substituent Effects on the Aromaticity of Cyclopropenium Analogues

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The cyclopropenyl ion and several of its derivatives have attracted the interest of experimental and theoretical chemists [1-3]. Aromaticity is of fundamental importance to chemistry [4]. Herein, we wish to report the structures, energies, and aromaticities of unsaturated three-membered rings with the help of the Gaussian 09 program using the B3LYP theory and the 6-311+G(d,p) basis set. Aromatic stabilization energies (ASE) were also evaluated from nucleus-independent chemical shift (NICS) values of title molecules. All of the studied compounds obey the rule of Hückel $(4n+2)\pi$ electron species. However, the inclusion of Si and Ge elements heavier than carbon decreases the aromaticity.

To what extent are the aromaticities of these three membered rings affected by their substituents? For this question, the effect of substitution of cyclic system can be quantitatively examined by sEDA and pEDA parameters. The calculated sEDA and pEDA descriptors correlated with NICS and ASE values.

X: Si and Ge
Y: -BeH, -BF_2, -BH_2, -Br, -CF_3, -CH_3, -Cl, -CN,
- F, -H, -Li, -NH_2, -NO_2, -OCH_3, -OH, -Ph,
-SCH_3, -SH, -SiH_3, $SiMe_3$, -*t*-Butyl.

*This work was supported financially by the Scientific and Technological Research Council of Turkey (Grant No. TUBITAK **TBAG 212T049**).*

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MOE interface for multidimensional MOPAC scan calculations using the example of prenylating enzymes.

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To date MOPAC [1] reaction coordinate calculations (scan) are rather difficult to prepare. The results, especially of 2D-scans, are arduous to visualize and interpret. Furthermore, fixing a high number of atoms, e.g. backbone atoms of an enzymes active site, is also not yet possible without rather high efforts. MOE already provides a simple interface for setting up MOPAC calculations. However, chemical or enzymatic reactions cannot be handled with this interface.

Here we report a compilation of svl scripts providing a MOE [2] interface for MOPAC 1D and 2D scan calculations. These scripts feature a GUI for simple creation of MOPAC input files and selection of reaction path parameters. Furthermore, it facilitates importing calculation results to molecular databases and simultaneous visualization of the energy hypersurface and corresponding molecular structures. Overall, these scripts provide some straight-forward extensions of the MOE built-in MOPAC functions especially regarding scan calculations. Functionalities of these scripts are demonstrated with the help of MOPAC scan calculations of the reaction path of a monoterpene synthase.

Comprising more than 60,000 compounds terpenoids form the largest family of natural products [3]. Monoterpene synthases catalyze the reaction of geranyl- or linalyl-diphosphate to a broad range of highly diverse monoterpenes. A high number of these enzymes produce a complex, yet specific, spectrum of products, which indicates a, up to some point, similar mechanism of formation of these products. Here the energetic level of the transition state of the respective reaction path decides which product is formed. MOPAC provides an engine for semi-empirical calculations, which are suitable for identification of these reaction paths as well as the corresponding transition states. The scripts mentioned above simplify input preparation and output analysis of MOPAC calculations.

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Modeling Charge Transport in SAM-FETs with Quantum Monte Carlo

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The description of charge transport in organic electronic devices [1] raises two major concerns: a proper description of the electronic system and a proper description of molecular motions.

In our multistep hierarchical modelling approach we begin with an extensive sampling of structural and dynamics information with classical Molecular Dynamics. Snapshots of these simulations are used to generate an electronic energy landscape (EA_L) [2] of the respective system.

In our poster we will focus on the method of exploring the EA_L maps with Agent-based Quantum Monte Carlo (MC) Simulations. In our simulations we describe the electrons (agents) with large amounts of interacting walkers, that move randomly, directed by energy minimisation and the Metropolis Test over the EA_L map. We use the semiempirical MNDO method to describe the interactions of the walkers.

The MC simulations will allow us to visualize and rationalize possible conducting paths, and by that link molecular structure to electronic functionality.

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Ion and pH Effects on Foam Protein Aggregation

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Second order spectroscopic techniques allow to selectively probe properties of molecules adsorbed to surfaces or interfaces, rather than bulk properties. Sum frequency generation (SFG) is used to study the proteins that stabilize foams formed by milk or whey, thus providing information on the order of the molecules adsorbed to the interface. [1,2] Additionally, ellipsometry provides information on the layer thickness of the adsorbed species and the oligomerization state of a protein in the bulk can be examined by analytical ultracentrifugation. However, many of the molecular details of the aggregation and surface adsorption process remain unclear. Here, we use atomistic molecular dynamics simulations to investigate aggregates of beta-lactoglobulin in aqueous solutions at different pH values and in different electrolytes.

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Determining the stereochemistry and key excitations in the CD spectra of organic molecules by theoretical methods

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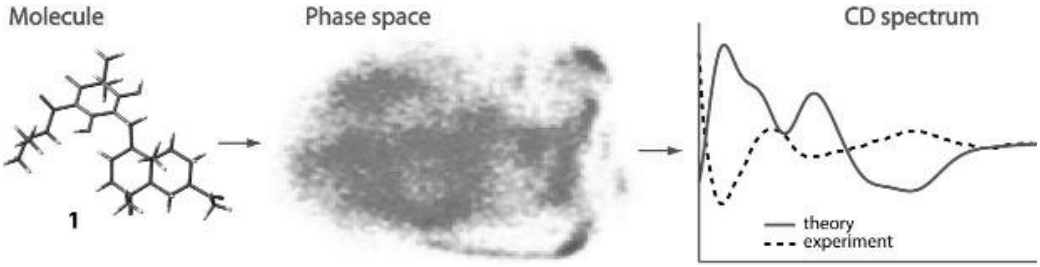

Circular dichroism (CD) spectroscopy is one of the most useful methods for the determination of the absolute configuration of optically active molecules, which represents one of the key aspects of molecular stereochemistry. However, since the CD spectrum strongly depends on the molecular flexibility of the involved chromophores, the interpretation of the experimental data is challenging. Hence, to properly assign the absolute configurations, theoretical methods need to be employed. In a recent study we have shown that a combination of replica exchange molecular dynamics, a clustering procedure, and TD-DFT methods can provide a general framework for the calculation of the CD spectra of flexible molecules [1]. We validate our methodology by finding excellent agreement with the experimental spectra of 3 novel terpenoid compounds of the rhodomyrtal family (such as **1**) for which we successfully determine the absolute configurations. We furthermore apply our method to flexible peptides and explore how the predominant amide and aromatic excitations shape the overall result.

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Modelling Self-Assembly of Phosphonic Acid on Aluminum Oxide Surfaces

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Modeling diffusion controlled processes such as crystal growth remains a challenging task in computational chemistry due to the large time scales. In the Kawska-Zahn approach – a combination of molecular dynamics and Monte-Carlo simulations – the growth is modeled in a

step-by-step process to overcome this problem. [1] In the present work, we present a slightly modified version of this method to investigate the formation of self-assembled monolayers (SAMs) of phosphonic acids on sapphire (0001) surfaces.

As surfactants we considered alkylphosponic acids of various lengths and phosphonic acids containing C60 moieties in different ratios as used by Halik et al. for the formation of self-assembled monolayer field-effect transistors (SAMFETs). [2]

By means of molecular dynamics simulations we demonstrate the gradual ordering of the surfactants during SAM formation, and explore structural/ectronic properties of the bulk Monolayers.

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Rigid-Body Molecular Alignment Using Quantum-Mechanics-Derived Local Properties

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Molecular alignment is an essential prerequisite for many ligand-based drug design (LBDD) techniques such as 3D-QSAR, pharmacophore elucidation, receptor modeling and 3D similarity searching. [1] Molecular alignment prior to these approaches represents an approximation to the binding orientation of the investigated ligands in the biological target, whose structure is unknown. The quality of the alignment greatly influences the results and performance of these LBDD approaches; for example the results of 3D-QSAR are very sensitive to the manner in which the different ligands are aligned. [2] We now present a workflow for rigid-body molecular alignment using quantum-mechanics-derived electron density (ρ) and molecular electrostatic potential (MEP) calculated on a grid around the ligands to be aligned. The alignment algorithm depends on maximizing the similarity between the template molecule and the other dataset ligands. The similarity between the two molecules' properties on the grid is calculated using Hodgkin's similarity index [3] and the Simplex algorithm [4] is used to maximize the similarity. The use of quantum-mechanics-derived properties makes this alignment protocol more accurate and more efficient in describing molecular steric and electrostatic properties than conventional molecular-mechanics-based methods, which use atom-centered charges and Lennard-Jones potentials. They consider important features for CADD which cannot be described by conventional methods such as σ-holes (responsible for halogen bonding) and polar flattening. Being field based, the method presented is efficient in aligning chemically diverse ligands and finding chemically different ligands with similar binding properties, an important feature for scaffold hopping and finding new chemical entities (NCE) to overcome patent limitations. Although it uses quantum-mechanics-derived properties, the method presented is computationally efficient and so it can not only be used for molecular alignment prior to 3D-QSAR or pharmacophore elucidation campaigns but also for 3D similarity searching in databases.

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Solvation effects on chemical shifts by 3D RISM theory

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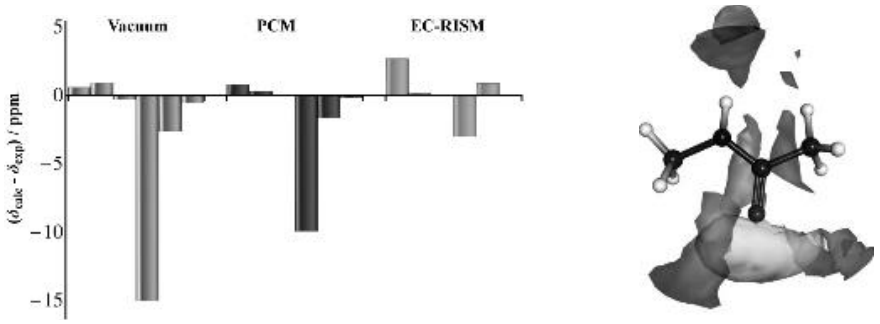
Accurate predictions of chemical shifts are relevant for the interpretation of nuclear magnetic resonance (NMR) spectra not only of small molecules, but even more so for structure predictions of bioorganic and polymeric entities since their chemical shift distribution increases in complexity due to the conformational freedom. In order to capture environmental effects adequately, quantum-chemical calculations of NMR parameters have to be combined with an accurate solvent model that reflects directional interactions such as hydrogen bonds that can have substantial influence on chemical shifts.



To retain the solvent granularity, which is neglected in continuum solvation models, we developed the "embedded cluster reference interaction site model" (EC-RISM) [1] that combines statistical-mechanical 3D-RISM integral equation theory and quantum-chemical calculations in a self-consistent manner. EC-RISM theory is capable of calculating thermodynamic quantities such as pK_a shifts and tautomer ratios [2,3] in aqueous and in nonaqueous solution with affordable computational costs. Here we use EC-RISM to increase the accuracy of quantum-chemical nuclear magnetic shielding calculations for small bioorganic building blocks in comparison with continuum solvation data and with results from computationally demanding cluster approaches combined with molecular dynamics simulations [4]. We discuss statistical evaluation schemes and illustrate the relation between chemical shift and solvent structure.

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Systematic investigation of protein-protein docking servers for auxin response related proteins

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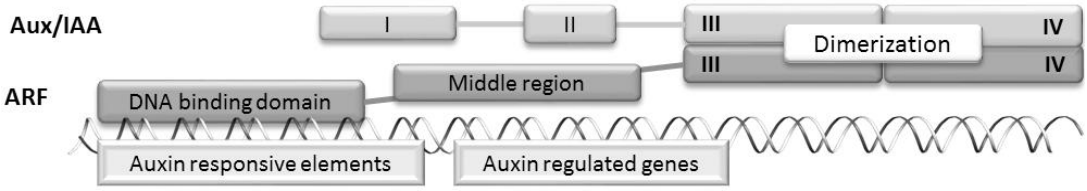
The control of plant growth and development is strongly regulated by and correlated to the response of the plant hormone auxin. In the hierarchical control of gene expression two plant protein families, Aux/IAAs (Auxin/Indol-3-Acetic Acid binding proteins) and ARFs (Auxin Response Factors), play an important role as transcription factors. The protein structures of both families consist of four domains, which contain a structurally similar protein-protein-interaction domain III/IV [1].



For these dimer domains there are no X-ray structures available. Therefore, insights into the most likely dimer arrangements should be derived from *in silico* homo- and heterodimerization (protein-protein docking) studies.

As a prerequisite for more detailed studies on the auxin related proteins, the most appropriate docking server programs should be identified. For this purpose two already known related heterodimer structures were used as test systems. The $p40^{phox}$-$p67^{phox}$-PB1 complex (PDB code: 1OEY [2]) and PKCι/λ-Par6α-PB1 complex (PDB code: 1WMH [3]) were split into monomers and used for protein-protein docking studies. ClusPro [4], GrammX [5], Hex [6], and ZDock [7] were tested with different parameters. All obtained dimer models were ranked and compared with interaction energies based on subsequent force field energy optimizations using Amber12:EHT. Finally, the RMSD (Cα) values between the dimer models and the X-ray structures were calculated.

As a result of these studies, Hex appeared as the most promising one. However, dimer arrangements with most negative interaction energies neither do correlate with those of the experimental structures nor with the best results from the server programs.

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Urotensin-Related Peptide (URP) Long-term Molecular-Dynamics Simulation

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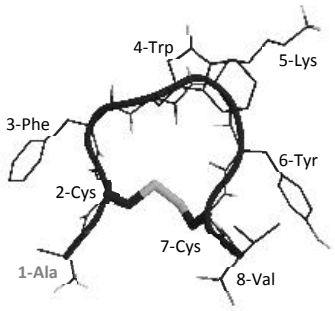

Urotensin-related peptide: Ala-[Cys-Phe-Trp-Lys-Tyr-Cys]-Val
(Human-UII: Glu-Thr-Pro-Asp-[Cys-Phe-Trp-Lys-Tyr-Cys]-Val)

The hormone peptides URP (urotensin-related peptide) and U-II (urotensin II) are the natural ligands of the urotensinergic GPCR (G-protein coupled receptor) system, which plays an important role in the regulation of the cardiovascular system. Besides their physiological function, URP and U-II are also linked to pathophysiological processes such as hypertension [1].
URP is an octapeptide with a six-residue ring closed by a 2Cys-7Cys-disulphide bridge, a 1-Ala N-terminal and an 8-Val C-terminal. URP differs from U-II only in the length of the N-terminal and is thus a prototype for the ring-system of these hormone peptides. Both the ring-residues Trp-Lys-Tyr and the disulfide bridge are thought to be important for receptor activation [1].
Understanding the dynamic conformational properties of URP can help develop pharmacophores and direct simulations of the receptor.
We describe a 5 µs molecular-dynamics simulation of URP that demonstrates the high flexibility of the peptide. *DASH* [2] analysis reveals several distinct main and transient conformational states that interchange rapidly. These states will be characterized and their properties discussed with some focus on the conformation of the disulfide bridge.

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Thermodynamic and kinetic ion selectivity of phospholamban

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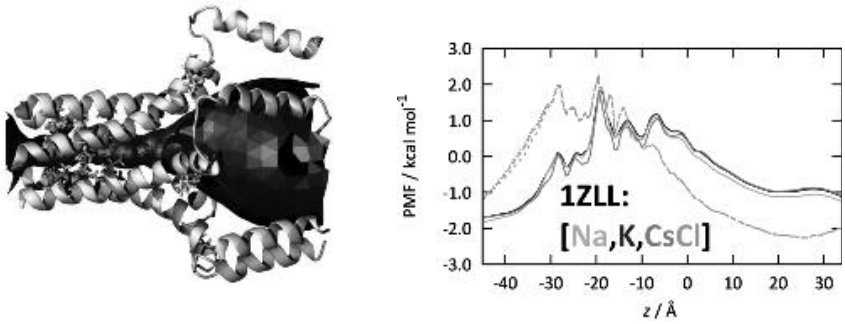
The membrane protein phospholamban is known to modulate the clearance of Ca^{2+} from the cytosol in muscle cells by blocking, in its monomeric form, the sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA). However, phospholamban also exists as a pentameric assembly whose function is controversially discussed. It might represent an inactive storage form but it was also demonstrated to function as a cation channel [1]. Structurally, a narrow hydrophobic constriction in the interior of the phospholamban pentamer forms an apparent barrier to ion translocation. Yet the protein apparently favors the larger Cs^+ over smaller cations.



Here we investigate into the ion translocation features by means of computations of the potential of mean force (PMF) at finite concentration conditions. The PMF is a key quantity for characterizing chemical and biological processes since it represents the free energy change along a given reaction coordinate. We employ the 3D reference interaction site model (3D RISM) integral equation theory, that yields correct K^+/Na^+ selectivity predictions for potassium channels [2]. In contrast to expensive molecular simulation approaches, 3D RISM theory allows for the direct, noise-free computation of the PMF in order to address the thermodynamic and kinetic ion preference of phospholamban for Cs^+, K^+ and Na^+. The link between PMF and ion conductance is provided by a simplified mean field theory [3].

The methodology is applied to two conformations of the putative phospholamban channel protein. We show that both thermodynamic and kinetic selectivity agree with experimental data from electrophysiology for one of the conformations treated (PDB code 1ZLL), while the other form (1XNU) is apparently impermeable. The calculations shed light on the molecular basis of phospholamban conductance by providing detailed maps of the PMF along the channel axis.

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On a Potential Sodium Effect in Fibrillar Amyloid-β Oligomers

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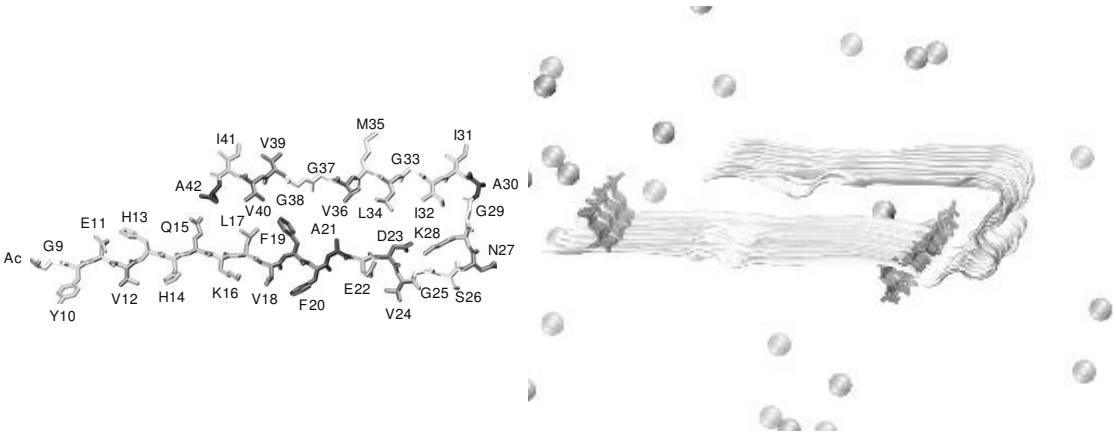
The aggregation of amyloid-β (Aβ) peptide into oligomers and fibrils is the hallmark in Alzheimer's Disease (AD). Nowadays, small soluble oligomers are believed to be the most neurotoxic species, probably the causative agents in AD. Aβ fibrils on the other hand may serve as reservoirs for small toxic oligomers. While it is well known from experiment, that the aggregation process is modulated by salt concentration in solution, the molecular details of the underlying interactions are not.

Salts occur ubiquitously in physiological environments and are known to have profound effects on the solubility of proteins (Hofmeister series). Monovalent alkali metal ions exhibit a more subtle effect on Aβ aggregation in experiment than doubly charged species [1,2].

In this contribution we investigate the so-called 'sodium-effect' on fibrillar Aβ oligomers. This effect modulates the self-organization of amphiphilic carboxylates in forming micelles: Na+ is able to form bridging complexes with carboxylate groups, in contrast to K+ [3].

A systematic series of molecular dynamics simulations of single and double layer fibrillar Aβ oligomers in aqueous 150 mM salt solution provides insights about the stabilizing interactions between the cations and charged Aβ key residues (e.g. Glu22). The current results show similarities and differences with a previous computational study, which lacked a physiological ion concentration in the solvent [4]. Interestingly, metal ions can access the water channel present in fibrillar Aβ species, which is located in the turn region. The ions use the same entry paths found previously for water molecules [4].

Furthermore, Na+ and K+ ions exhibit a different interaction behaviour with the fibrillar Aβ oligomers. This suggests the existence of a sodium effect in this species.



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Molecular Modelling Studies on Farnesyltransferase Inhibitors

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Farnesyltransferase (FTase) is one of the targets in the development of potential anticancer drugs. Recently, it could be an effective target for drug development against Progeria and parasites diseases such as *P. falciparum* resistant malaria, trypanosomatid infections (African sleeping sickness), Chagas disease, Toxoplasmosis and Leishmaniasis and as antiviral agents [1,2]. In the present investigation, we have performed docking and molecular dynamic (MD) simulation on different FTase enzymes (with and without the farnesyl pyrophosphate (FPP) substrate). In addition, protein ligand interaction fingerprint (PLIF) analysis was performed on different docked conformations of a data set of natural products. The zinc ion in the FTase makes coordination bonding with residues such as Asp297, Cyp299 and His362 in B chain. The MD simulation performed on 10 ns showed that the drug complex is stable.

The docking analysis revealed that the positively charged groups on the active site of the enzyme or receptor (possibly the Arg202β amino acid residue and the Zn^{2+} ion), form hydrogen bonds with negatively charged groups (keto, hydroxyl, amino and heterocyclic rings) in their structures. The aromatic rings present in the natural product compounds have make pi-pi interaction with the aromatic amino acids (Tyr363, Tyr302 and Trp305 (without FPP) and Tyr361, Trp303 and Tyr300 (presence of FPP)).

These analyses highlighted that Chaetomellic acid A and B, Zaragonic acid, Arteminolide, etc have better inhibitory activities and bind significantly to the active site [1,3]. The PLIF analysis also confirms that the binding modes of the studied compounds are follows the same pattern as the compound in the PDB structure. Those compounds have fused ring system and more branched structures have better docking score. In order to confirm the binding behavior of the compounds molecular dynamic simulations is performed on the compounds. These studies provide some lead compounds for the development of novel bioactive molecules.

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Active-state model of a dopamine D_2 receptor - $G\alpha_i$ complex stabilized by aripiprazole-type partial agonists

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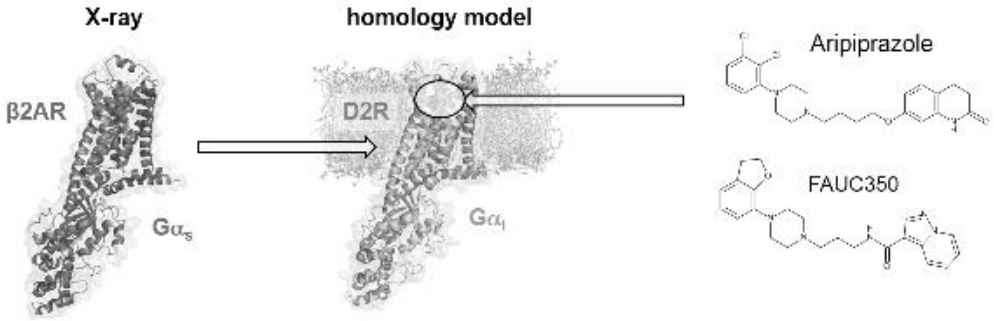
Partial agonists exhibit a submaximal capacity to enhance the coupling of one receptor to an intracellular binding partner. Partial agonism at dopamine D_2 receptors (D2R) has been suggested to exert beneficial effects on schizophrenia, a chronic mental illness characterized by hypo- and hyperfunctions in monoamine neurotransmitter systems including mesolimbic and mesocortical dopaminergic pathways [1]. Due to their stabilizing effect on monoamine pathways, especially the dopaminergic pathways, dopamine receptor partial agonists such as aripiprazole represent promising options for the treatment of schizophrenia [2,3].

To understand the structural determinants of partial agonism better, we performed molecular-dynamics simulations employing our recently described active-state homology models of the D2R-$G\alpha_i$ protein-complex [4] coupled to the partial agonists aripiprazole and a closely related compound, FAUC350, and compared the impact of these ligands on the conformation of the ternary complexes with those of previous simulations with the full agonist dopamine.

We found that the two partial agonists are capable of differently regulating the shape of structural motifs, including the extracellular loop regions, the binding pocket and, in particular, intracellular G protein-binding domains. As G protein-coupling to certain intracellular epitopes of the receptor is considered to be the key step of allosterically triggered nucleotide-exchange [5], it is tempting to assume that impaired receptor-G protein-coupling due to distinct ligand-specific conformations is a major determinant of partial agonist efficacy.



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Development and validation of MM-(GB)SA models for predicting the biological activity of sirtuin inhibitors

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Silent information regulator 2 (Sir2) proteins, also named sirtuins (SIRTs), are NAD+ dependent histone deacetylases distributed in lifeforms ranging from prokaryotes to eukaryotic organisms. To date seven sirtuin subtypes have been identified in humans; SIRT1-7 that share a highly conserved catalytic NAD+/acetyl-lysine binding site. Human sirtuins SIRT1-3 represent interesting targets related to the treatment of age related diseases, neurological disorders (like Parkinson`s and Alzheimer`s diseases), metabolic syndromes (such as diabetes and obesity), viral diseases and cancer [1, 2]. Most of the sirtuin modulators that have been identified so far show limited potency and/or isoform selectivity. Therefore, the development of potent and specific inhibitors of sirtuins might help to evaluate their pharmacological potential for several diseases and exploiting their functions in cellular processes.
In order to rapidly screen large compound databases, docking-based virtual screening (VS) approaches have been used to predict the binding strength of ligands. However, current scoring functions show a poor correlation with biological data and more rigorous methods are in need. In this study, we present an MM-(GB)SA approach that can be used as an effective post-docking filter tool to enrich VS results and prioritize hits for further biological testing.

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In silico predictions of drug-drug interactions caused by CYP1A2, 2C9 and 3A4 inhibition – a comparative study of virtual screening performance

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Investigation of the clearance pathway is nowadays an integral part in early drug development, since alteration of metabolic enzymes can markedly influence the toxicological profile and efficacy of novel compounds. The cytochrome P450 (CYP) superfamily represents the major enzyme class responsible for the metabolism of exogenous compounds. Within this study, the three isoforms CYP1A2, 2C9 and 3A4, which account for approx. 70% of oxidative drug modifications [1,2], were investigated with several *in silico* methods including pharmacophore modeling [3,4], shape-based screening [5,6], docking [7], and 2D-similarity based comparison. [8,9] We generated multiple *in silico* models for the three isoforms using every method and investigated their ability to predict the inhibitory potential of compounds from our inhouse-database. After subsequent biological confirmation of the *in silico* predictions, we could analyze and compare the prospective performance of all methods, thereby defining the suitability of the applied techniques for CYP enzymes. While some software tools failed, others appeared to be of high relevance for the prediction of drug-drug interactions and may therefore be a valuable prioritization tool for planning experimental testing in drug development.

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Conformational and tautomer sampling of small molecules in solution with quantum-chemical accuracy

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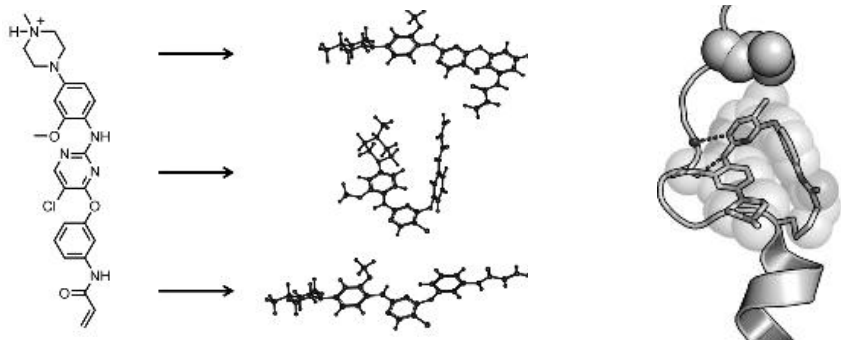
High-throughput screening of the tautomer and conformational space of small drug-like molecules in solution provides important information for molecular design. In particular, predicting and controlling free ligand conformations is essential for minimizing the entropic penalty to reorganize a ligand's geometry upon binding to a protein. Overcoming the deficiencies of common small molecule force fields represents a particular challenge due to the considerable computational cost of high-level quantum-chemical calculations for predicting tautomer prevalence and the conformational manifold.

Here we demonstrate the performance of a hierarchical filtering scheme that allows for the identification of dominant tautomers and conformations together with their proper statistical weight measured by their free energies in solution with quantum-chemical accuracy. The automated workflow implies a sequence of force field-based high-temperature molecular dynamics simulations using implicit solvent models, clustering and filtering steps, and high-level geometry optimizations in solution employing the polarizable continuum model (PCM) as well as the embedded cluster reference interaction site model (EC-RISM) [1] for final scoring.



As proof of concept, we apply the workflow to protein kinase inhibitors where a conformational pre-arrangement has a dramatic influence on the inhibitory efficacy. In particular, we focus on WZ4002 that is known as a highly active kinase inhibitor for the drug-resistant mutant of the epidermal growth factor receptor (EGFR T790M) [2]. EGFR and its mutant variants play an important role in non-small cell lung cancer (NSCLC). WZ4002 is a suitable candidate for this approach since its binding mode in the active site of the protein and with it the ligand's geometry is known from the X-ray complex structure. We discuss implications for gaining valuable insights into the significance of the substitution pattern at pivotal ligand regions with the intention to adapt this approach to further kinase inhibitor scaffolds.

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Conformational stability and oligomerization properties of the viral GPCRs US27 and US28

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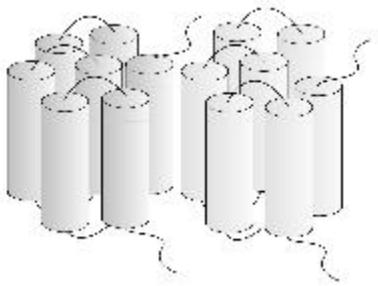
Communication is a basic task in everyday's life and even the smallest compartments of multicellular organisms have to communicate with each other. Eukaryotes developed, among others, G-protein coupled receptors (GPCR) that can be activated by a ligand outside the cell and trigger a mechanism inside the cell.

The human cytomegalovirus (HCMV) encodes four GPCRs: US27; US28; UL33; and UL78 that are known to interact with human cell receptors like CXCR4. Moreover, the viral GPCR US27 can dimerize with CXCR4 and thereby influence CXCR4's signalling behavior. It is also known that US28 can form a homodimer and a heterodimer with US27; whether this dimerization has an effect on host cell receptor signalling is still unknown.



The purpose of this study is to better understand the interactions between human and viral GPCRs. The structures of the viral GPCRs were modelled based on the 3D structure of the homodimer CXCR4. Subsequent structural analysis was be performed to assess the role of individual residues for dimer formation. In the end, this study should help experimental researchers to have a clue about protomer properties of dimerization and important residues that might be used for mutational studies.

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Understanding adsorption in Zr-organic frameworks: A computational study

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Metal-organic frameworks (MOFs) represent a class of porous materials that have emerged as an important new class of crystalline materials over the last decade. These compounds are assembled from organic molecules as linkers and metal clusters as joints resulting in robust frameworks. Depending on the choice of the linker molecule, pore sizes can be engineered for a wide range of applications like gas storage, catalysis or in biomedicine. PIZOFs (porous interpenetrated Zr-organic frameworks) are a class of two-fold interpenetrated Zr-MOFs, the internal voids can be tailored in a wide range by changing the substituents of the central phenylene ring of the organic linker molecules (PIZOF structure with an accessible pore highlighted by sphere (a) Rod-like PIZOF-linker with side chains R^1 and R^2 (b), Fig. 1).[1]

a) b)

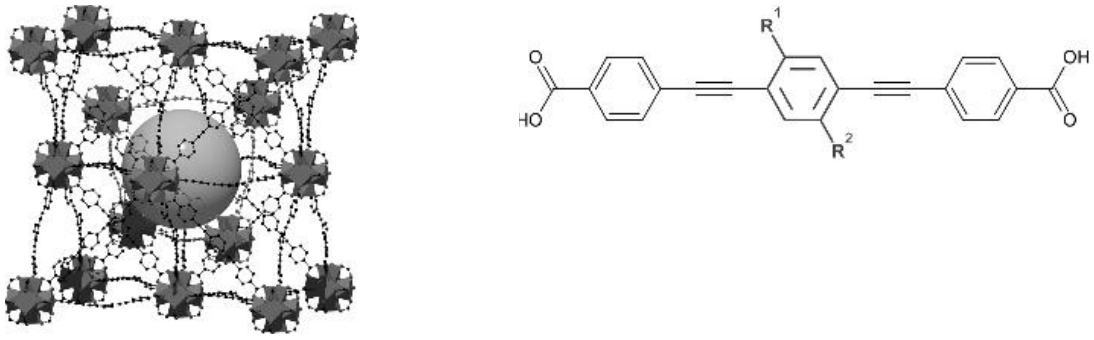

Figure 1

Grand Canonical Monte Carlo (GCMC) simulations were performed on different PIZOFs and other Zr-MOF compounds [2] to investigate the adsorption of various adsorptives (Argon, Nitrogen, Carbon dioxide, Methane). However, it turned out, that the choice of the partial charges is crucial for the simulation results. In this work, we present DFT calculations on clusters cleaved from the unit cell of each MOF structure. The electrostatic potential charges obtained with MERZ-SINGH-KOLLMAN (MK) scheme were used to determine the atomic charges. We present a molecular model that predicts the shape of the isotherms mostly in good agreement with experimental data and helps to explain the adsorption mechanisms that are responsible for this behavior.

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The Electronic Structure of Amorphous and Graphitic Carbon Nanoparticles

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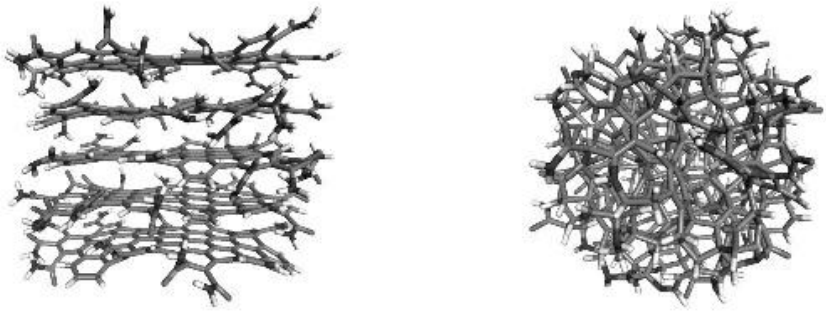
Carbon nanodots (CNDs) can easily be synthesized from small molecules and feature interesting properties, most prominently strong, tunable photoluminescence and high water solubility. The structure of these materials is difficult to study experimentally because the particles are usually quite polydisperse. Additionally, CNDs consist exclusively of light elements (C,N,O) with low scattering cross-sections towards electron and X-ray radiation, limiting the use of many important characterization methods (e. g. TEM, XRD).



We have developed two distinct structural models for CNDs. On the one hand, we constructed heavily functionalized graphene/graphite particles. On the other hand, we considered amorphous carbon spheres with relatively low density, which feature a considerable amount of sp^2 atoms. In this case the role of nitrogen impurities was also investigated. To study the geometry and electronic structure of these models (which consist of thousands of atoms), we relied on the massively parallel semi-empirical molecular orbital theory program EMPIRE.[1]

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Ab Initio Modeling of Calcium Channel Voltage-Sensing Domain

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Voltage-gated calcium channels are involved in several diseases and, consequently, constitute a target for many drugs. Since they are membrane proteins, 3D structures are difficult to obtain through crystallization; hence, up to now, their mechanism is not completely clear yet and further studies are necessary to better understand their functions and modulation.

In particular we focused on $Ca_v1.1$ alpha1 subunit to investigate the voltage-sensing domain and the implications of mutations for voltage sensitivity [1]. Since no crystal structures are available on the Protein Data Bank and the sequence identity between calcium and other ion channels is too low to use homology modeling, we generated models through ab initio modeling. We applied the Rosetta method [2] to generate 3D structures of native and several mutated channels, and then compared our results with experimental data.

As known from sodium and potassium channels [3], positive-charged residues in transmembrane segment S4 of alpha1 subunit have a central role in channel opening; in detail we investigated the S3-S4 loop and D1196 involvement in voltage sensitivity. We demonstrate how structural models can be helpful in the interpretation of complex assay data.

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The hpCADD NDDO-based Polarizable Force Field: Classical Force-Field Potentials and Parameterization

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We present the second part of the parameterization of the new ***hpCADD*** polarizable force field. Since the electrostatic interaction between drug-molecule and its target plays a crucial role in Computer-Aided-Drug-Design (CADD), the quality of a force field is linked to its ability to represent such interactions as accurately as possible. In many cases, atom-centered monopole charges are not able to represent the molecular electrostatic potential (MEP) accurately enough. A far better way to describe the MEP is to use atom-centered multipoles derived from semiempirical molecular-orbital (MO)-theory. [1,2]

The new ***hpCADD*** force field now combines electrostatics (Coulomb and exchange) taken from a specially parameterized NDDO wavefunction directly with classical force field potentials for an accurate representation of structures and relative energies.

In the first step, the semiempirical NDDO-Hamiltonian was parameterized in order to represent the *ab initio* (MP2/aug-cc-pVDZ) molecular electrostatic potential (MEP) at the 0.01 a.u. electronic isodensity surface of the molecule accurately. [3]

We now describe the second step, in which the classical force field potentials were parameterized while keeping the NDDO-based Coulomb and exchange interactions fixed. Classical harmonic bond-stretch and angle-bend potentials were used with Fourier series torsional potentials, a correction potential for electronic interpenetration (i.e. a short-range correction to the multipole approximation) and an undamped dispersion term.

The performance of the new force field for hydrocarbons will be demonstrated.

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The HPA-1 polymorphism impacts the platelet-specific integrin $\alpha_{IIb}\beta_3$ by a ripple effect

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The human platelet antigen (HPA)-1 alloimmune system is a biallelic system carried by the megakariocyte/platelet specific integrin $\alpha_{IIb}\beta_3$, which mediates platelet adhesion and aggregation; it is essential for hemostasis but can also foster thrombus formation. The HPA1 polymorphism of $\alpha_{IIb}\beta_3$ arises from a leucine-to-proline exchange at residue 33 of the mature β_3 subunit resulting in HPA-1a (Leu33) or HPA-1b (Pro33) platelets [1]. Genotyping revealed that patients with coronary artery disease who carry the HPA-1b allele experience their myocardial infarction 5.2 years earlier than HPA-1a/1a patients [2]. It has been postulated that integrin exists in two main and mutually exclusive conformations; the bent, closed form, and the unbent, open structure. Local and global structural rearrangements are required in going from the closed to the open form, thereby leading to integrin activation. While the experimental observations have shown that HPA-1b (Pro33) is a prothrombotic variant of $\alpha_{IIb}\beta_3$, it has remained elusive so far how the mutation, located more than 90 Å away from any of the binding sites of the integrin, contributes to the heightened activatability of the integrin.

In the present study, the ectodomains of the two $\alpha_{IIb}\beta_3$ variants in the closed conformation were used as model systems, and the consequences of the Leu33Pro substitution on the structure and dynamics of the integrin were analyzed through molecular dynamics (MD) simulations of in total 3 μs length. In atomic detail, comparative analyses of the trajectories revealed that Leu33 is involved in stabilizing interactions connecting the PSI domain in the head region of integrin and the nearby EGF-I and EGF-II domains in the leg region of the β-subunit. The absence of this network of interactions in the Pro33 variant destabilizes the β-subunit. The resulting local instability percolates through the structure and leads to the system being globally less stable; this fosters a heightened activatability. In good agreement with experimental observations, these findings explain how the fine-tuned conformational equilibrium of the integrin can be allosterically influenced by a distant mutation.

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An inverse docking approach for identifying new potential anticancer Targets

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Abstract

Inverse docking is a relatively new technique that has been used to identify potential receptor targets of small molecules. Our docking software package MDock is well suited for such an application as it is both computationally efficient, yet simultaneously shows adequate results in binding affinity predictions and enrichment tests. As a validation study, we present the first stage results of an inverse-docking study which seeks to identify potential direct targets of PRIMA-1. PRIMA-1 is well known for its ability to restore mutant p53's tumor suppressor function, leading to apoptosis in several types of cancer cells. For this reason, we believe that potential direct targetsof PRIMA-1 identified *in silico* should be experimentally screened for their ability to inhibitcancer cell growth. The highest-ranked human protein of our PRIMA-1 docking results is oxidosqualene cyclase (OSC), which is part of the cholesterol synthetic pathway. The results of two followup experiments which treat OSC as a possible anti-cancer target are promising. We show that both PRIMA-1 and Ro 48-8071, a known potent OSC inhibitor, significantly reduce theviability of BT-474 breast cancer cells relative to normal mammary cells. In addition, like PRIMA-1, we find that Ro 48-8071 results in increased binding of mutant p53 to DNA in BT-474cells (which highly express p53). For the first time, Ro 48-8071 is shown as a potent agent in killing human breast cancer cells. The potential of OSC as a new target for developing anticancer therapies is worth further investigation.

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Keywords

Inverse Docking; *In Silico* Screening; Protein-Ligand Interactions; Molecular Docking

Do we need to analyze µs MD simulations differently?

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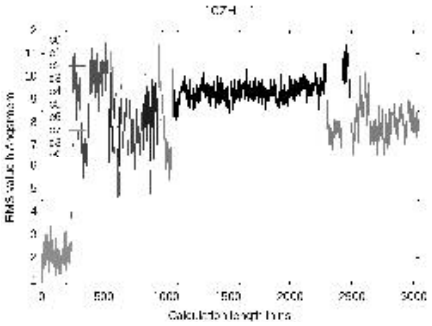
Biologically relevant timescales of 1 µs and more are becoming accessible in MD simulations because of the continuing increase in computational performance. Among the available methods for sampling the conformational space associated with such timescales, the brute force method has the advantage of being highly analogous to the actual processes and using little *a priori* knowledge [1]. We now present some methods that are useful for interpreting the vast amount of data associated with these kinds of simulations.



The system under investigation, the p53 core domain, has several flexible regions, as can be seen directly from B-factor plots. After cluster analysis of six 2 – 4 µs simulations, and comparison of the representative structures via the RMSD matrix, it is apparent that still no structural convergence is reached.

Subsequently, individual flexible regions were investigated. A set of cluster analyses was performed, in each of which only residues of one individual region were regarded (example shown in the left picture). Hydrogen-bond analyses can show structural homogeneity within clusters of those individual regions (example shown in right picture), as well as among clusters with similar representative structures. They can also show structural differences between clusters with high RMSD differences and thermodynamic explanations for sudden changes in the RMSD trajectory of the respective region.

For flexible loop regions, clustering by means of a DASH analysis, which is based on internal coordinates [2], also shows a good match to the results of Cartesian clustering based on atomic positions.

These analyses show that the ensembles obtained with cluster analysis indeed represent discrete conformations. The vastly simplified data provided by cluster analysis can be used to investigate individual regions systematically and identify reoccurring structures. In the p53 core-domain system, frequently reappearing structures are found in some of the flexible regions. While still not converged, the conformational space of these regions is thought to be sampled to a larger extent, compared to other regions or the whole protein domain.

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Conformational variability of the p53 core domain

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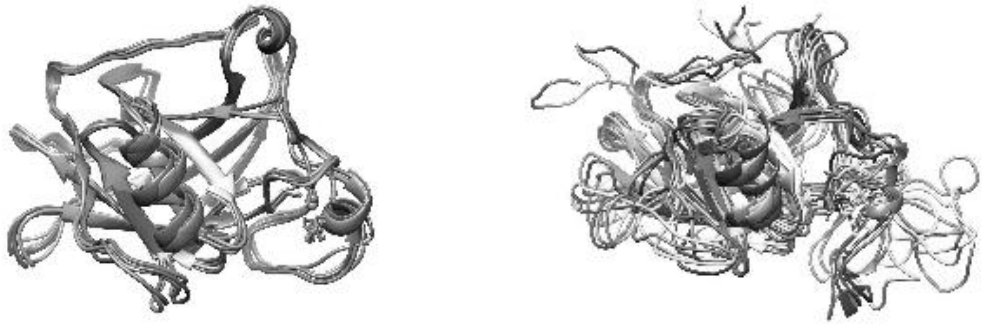
The tumor suppressor protein p53 has been widely studied because of its high mutation rate in human cancer cell lines. When intact, it acts as a transcription factor within a complex protein-signaling network, to control DNA damage repair, senescence and apoptosis. P53 has N-terminal and C-terminal unstructured regions to facilitate interaction with many different molecules, whereas the DNA binding domain is intrinsically ordered.

Many crystal structures are available for the p53 DNA binding domain in isolated form and in complex with a variety of other macromolecules [1-6]. From different crystal structures, six molecular-dynamics simulations were started and run for several microseconds each.



Compared with the different crystal structure starting points (overlay in left picture), a much greater structural variety is observed during the simulations (overlay in right picture). By analyzing the flexible regions of the protein domain separately with cluster analysis techniques, numerous intermittently stable conformations can be found. The structures of some flexible regions reappear during the simulations, whilst the vast majority of structures for other regions are formed only once. It is assumed that a larger part of the conformational space was sampled for flexible regions with reappearing structures, compared to regions without reappearing structures. However, the existence of additional conformations is considered very likely for each of the flexible regions.

In summary, there are several regions within the DNA-binding domain of p53 that have a much higher flexibility than can be seen in crystal structures. During their movement, they still form intermittently stable conformations.

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Hydration Properties with Polarizable Multipole Force Fields

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During the last decades, deficiencies of classic biomolecular force fields (fixed point charge, no polarization) have become increasingly evident. Therefore, new types of next-generation force fields that include terms for polarizability and anisotropic charge distribution such as AMOEBA (Atomic Multipole Optimized Energetics for Biomolecular Applications) have become increasingly more important. In order to enhance the performance of classical (fixed point charge) force fields, a new treatment of the electrostatics is crucial. Fixed multipoles as a higher basis set for the description of the electron density on each atom provide access to a better representation of the electrostatic properties of a molecule. In this work, we use the AMOEBA force field, which covers polarization effects through an induced dipole on every atom [1]. Polarization effects, which are not covered by conventional force fields, are of major interests as atoms are able to react upon their environment [2] resulting in a force field which can in an ideal case be used to describe molecules in both gas- and condensed phase.

In this work the differences between polarizable multipole force fields and conventional force fields regarding the description of ions in water were investigated. Ions and charged residues play a significant role in biomolecular interaction. The ion in water problem has a spherical symmetry and due to this symmetry properties like radial distribution functions (RDF) can easily be calculated and compared to reference methods. As a first test case for validating the improvement of the physical model we compared the RDF distributions for ions in solution obtained with AMOEBA and conventional force field calculations to those from QM/MM simulations.

Our initial results show that this new generation force field is describing the first hydration shell of ions better than conventional ones. Especially for negatively charged ions and divalent cations, polarizable force fields yield coordination numbers and RDFs which are closer to reference values than the standard AMBER water models tip3p, tip4p or tip5p.

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Formation of $Pt^{II}(DACH)Cl_2$ from $Pt^{IV}(DACH)Cl_4$ in the presence of dGMP. DFT study

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Platinum (II) complexes are some of the most used anticancer drugs. Nevertheless there is an effort to discover new compounds which have smaller side effects and are simultaneously active in the treatment of recently resistant tumors. Pt(IV) complexes represent such a class of drugs. However they must be initially reduced to Pt(II) analogues in an organism to reach their anticancer activity [1], but the reduction mechanisms are still not well-known.

In this study we focus on the reduction mechanism of $Pt^{IV}(DACH)Cl_4$ (DACH= diaminocyclohexane) in the presence of 5'-dGMP (2'-deoxyguanosine-5'-monophosphate) and 3'-dGMP, which was suggested by experimenters (shown at Fig. 1). [2] At first a chloride ligand in the complex is substituted by dGMP which leads to a formation of Pt-N7 bond. The reaction continues with nucleophilic attack of the phosphate or hydroxyl group at C5' end to the C8 position. Consequently the complex is reduced to $Pt^{II}(DACH)Cl_2$. The last step represents a hydrolysis of C8-O bond leading to a formation of 8-oxo-dGMP.

We studied geometry parameters of all species involved in this quite complex mechanism and changes in the electron density distribution. Explored structures were optimized at the DFT level with B3LYP functional in 6-31G(d) basis set and CPCM/Klamt solvation model. The energy parameters for the whole reaction were determined using the single-point calculations at the DFT level B3LYP-GD3BJ/6-311++G(2df,2pd) with IEFPCM/scaled-UAKS solvation model developed in our laboratory recently [3].

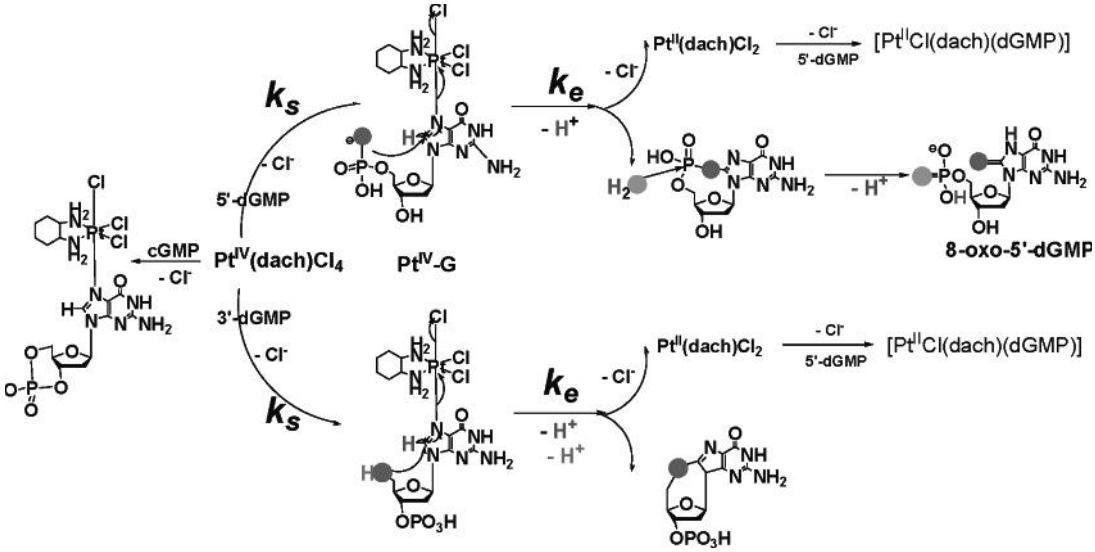

Fig. 1: Scheme of the explored reaction (taken over from [2])

Acknowledgements: Support from GAUK grant No. 532212 is acknowledged. The access to the METACentrum supercomputing facilities is acknowledged.

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Cubic C8 – An Aromatic Carbon Cluster?

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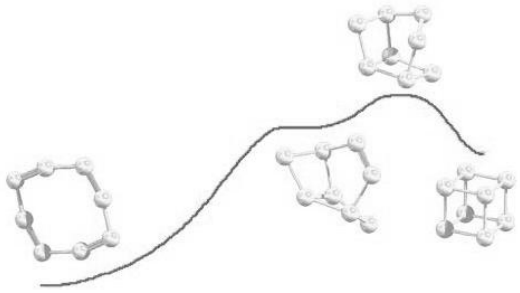
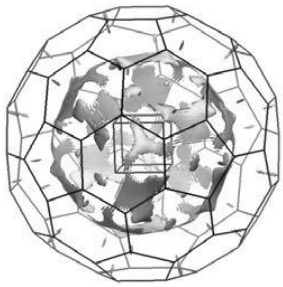
The cubic C_8 unit is represents the proposed primitive cell of the high-density carbon allotrope first described in 1978. Cubic C_8 and its isomers have been the subject of several theoretical studies.[1,2,3,] This cluster obeys Hirsch's $2(N+1)^2$ rule of spherical aromaticity. According to our high-level calculations O_h-symmetrical C_8 is a relatively stable strained cluster. The bond length is quite independent of the calculation level but unusually sensitive to the basis set used and varies between 1.47 and 1.51 Å. The lowest frequency normal vibration calculated with different levels of Møller–Plesset perturbation theory is degenerate and inconsistent with the results of coupled-cluster calculations.

The calculated electron affinity of cubic C_8 is 69 kcal/mol and ionization potential over 226 kcal/mol. The singlet-triplet gap is 17 kcal/mol, both the triplet and the cation radical are Jahn-Teller species with D_{2h} and D_{4h} symmetry, respectively. The cubic cluster is 100 kcal/mol more strained than the global minimum (C_{4h}-symmetrical ring) and can transform to it with a 62 kcal/mol barrier.



Rearrangement pathway



Non-covalent interaction in C8@C80

The exothermic reaction of C_8 with $^3O_2$ has a low barrier; 7 kcal/mol. The product is a triplet peroxide (energy gain 13 kcal/mol in comparison to separated molecules). The next step of the oxidation sequence is formation of dioxetane cycle, breaking of the propellane bond (to form a molecule familiar as to 9,10-dioxa-perdehydro-basketane) and further fragmentation. The barrier of this process is around 24 kcal/mol and is followed by spin-crossing from the triplet to the singlet state.

The cubic C_8 cluster can be encapsulated in C_{60} and C_{80} fullerenes (Russian doll structures), accompanied by strong electron transfer from C8 to fullerenes.

UV-spectra predicted by TDDFT and CASPT2 approaches are rather similar and exhibit peaks near 6.0, 7.9, 8.5, and 9.0 eV.

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H238N Mutant of Hsp47: Molecular Mechanism of Disrupted Collagen Binding

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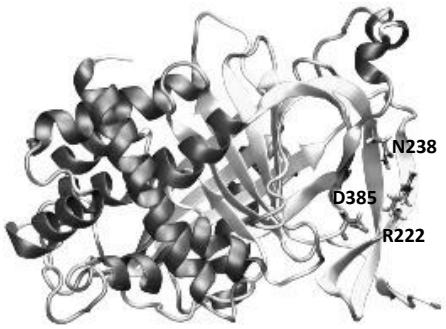
Heat shock protein 47 (Hsp47) is a molecular chaperone for collagen in humans. Although molecular chaperones typically recognize and bind nascent polypeptide chains and partially folded intermediates of proteins,[1] the Hsp47 molecule recognizes the folded conformation of collagen triple helices. Hsp47 can bind pH-sensitive to several types of collagen recognizing an arginine at the Yaa-position of a Xaa-Yaa-Gly triplet.

With the help of the crystal structure of Hsp47 in complex with trimeric collagen model peptides, it was shown that Hsp47 docks via a salt bridge to collagen.[2] This salt bridge is formed between the strictly conserved aspartate residue D385 of Hsp47 and the important arginine in the Xaa-Arg-Gly triplet. In addition to that salt bridge, the collagen interacts with the arginine residue R222 of Hsp47 via a hydrogen bond. Due to the fact that the collagen release from Hsp47 takes place in the *cis*-Golgi or ER-Golgi intermediate compartment and probably is accomplished by the lower pH in the Golgi compared with the ER, a pH-dependent substrate release mechanism based on a cluster of histidine residues was proposed.[2]



For the investigation of the pH-dependency of the collagen binding, the H238N mutant of Hsp47 was generated. However, the H238N mutant is not able to bind collagen. In order to investigate that unexpected experimental result, we performed constant pH MD simulations of the wild type and mutant form of Hsp47. The key finding is that the residues R222 and D385, which are involved in collagen binding in the wild type, are locked in an intramolecular salt bridge in the H238N mutant. This result offers a potential explanation for the behavior of the mutant on an atomic level.

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Unexpected Effect of Somatic Mutations on the Affinity of an Antibody by Altering Its Dynamics

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Human cytomegalovirus (HCMV) causes life-threatening infections in immunocompromised patients such as newborns, transplant recipients and HIV-infected patients. Spindler et al. recently characterized several neutralizing antibodies that bind Domain-II (DOM-II) of Glycoprotein B, which is an essential protein for the fusion machinery of HCMV. [1]

A recent crystal structure of the strongest binding antibody (SM5-1) in complex with DOM-II revealed that numerous residues emerging during affinity maturation do not directly interact with DOM-II. In particular, some polar amino acids in the CDR-H1 and CDR-H3 only form intramolecular interactions, thereby possibly playing a role in the stabilization of the antibody scaffold itself.

To investigate these interactions and the impact of somatic mutations on the dynamics of SM5-1, molecular dynamics (MD) simulations were performed for SM5-1 and a 6-fold mutant, in which 6 polar residues in CDR-H1 and CDR-H3 were exchanged to match less matured antibodies. This was done for the bound and unbound conformation of SM5-1 resulting in a total of 4 simulations. All MD simulations were performed with AMBER 11, the parm99SB force field, and in an octahedral box of explicit solvent for 100 ns.

Comparison of the dynamics of SM5-1 with the 6-fold mutant revealed that the mutations mainly enhance the flexibility of the long CDR-H3 loop both in the bound and unbound conformation. This higher flexibility in the 6-fold mutant can be attributed to the loss of important stabilizing interactions of the anchor region of CDR-H3.

Our studies show that somatic mutations within CDRs do not necessarily optimize only the direct antibody binding interface. In addition, such mutations can also have an indirect effect on the binding competent conformation of the antibody, thus increasing its affinity. Therefore, our findings have implications for other areas of computational research such as docking: It underscores the difficulty of predicting antibody-antigen structures since these approaches frequently consider residues, which have emerged during affinity maturation, as part of the interface. Consequently, in a case like SM5-1 and DOM-II they will fail to predict the right solution.

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Extension of molecular fragment based mesoscopic simulation to the biopolymer realm

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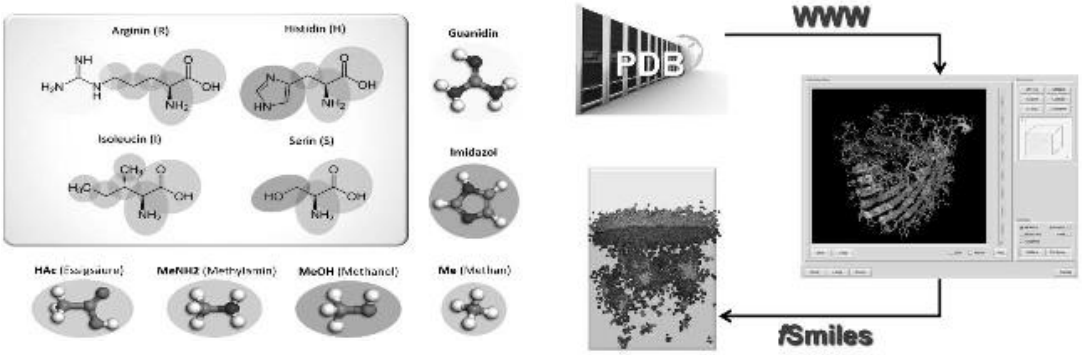
Dissipative Particle Dynamics (DPD) is an established simulation technique allowing the study of condensed matter on mesoscopic scales. Whereas its coarse-grained interacting units (beads) do not necessarily depend on distinct chemical compounds at all, the DPD variant Molecular Fragment Dynamics (MFD) makes use of specific molecules or molecular fragments. Recently MFD has been successfully applied for studying surfactant systems at the water-air interface [1]. This work aims at extending the MFD technique to the biopolymer realm of peptides and proteins.

To apply the MFD technique to biopolymers an adequate molecular fragment based description and an user interface for visualizing and editing the peptide or protein structure is required. The biopolymers are constructed from molecular fragments for all 20 proteinogenic amino acids including their charged species and disulfide bonds. The left figure shows the fragmentation scheme of selected amino acids. The editor allows the manual input of biopolymers from one-letter or three-letter amino acid codes. Additionally, for proteins the amino acid sequences and spatial data can be obtained from the Protein Data Bank (PDB) [2] (right figure). The visualization of structural data is based on Jmol [3]. All conversions are performed automatically including charges and spatial information.



MFD approximates the anisotropic molecular interactions in form of isotropic repulsion parameters. Since the structure of proteins is stabilized by anisotropic interactions like hydrogen bonds specific intramolecular potentials between fragments are defined to allow a flexible adjustment of the stiffness of the protein backbone.

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Optimization of post-docking strategies for hit identification of HCV NS5B polymerase inhibitors

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NS5B is an RNA-dependent RNA polymerase (RdRp), a key enzyme in HCV replication process, and a well validated drug target[1]. In an effort to establish an efficient for computational screening of HCV polymerase inhibitors, we tried a systematic combination of docking and post-docking strategies. Glide standard precision (SP) docking which allow flexible hydroxyl groups was applied to a set of known inhibitors [2]. We present an evaluation of 3 post-docking strategies including random forest (RF) classification, structural interaction fingerprint (SIFT)[3], and incorporation of docking to dummy binding sites. Random forest, an ensemble leaning method, was trained by 397 known inhibitors and used to build two models. RF model-1 predicted the compounds to bind or unbind and model-2 classified the compounds into potent or weakly actives. Structural interaction fingerprint was used to compare the interaction similarity of a given compound to the known inhibitors. But instead of one to one comparison between two molecules, we derived conserved interaction patterns from 29 crystal structures and used those as references. The last strategy called "two sites docking", compared the docking to a target site with docking to a dummy binding site. Both binding sites show different binding site structures. The compounds which scored well in both binding sites were discarded. This strategy was based on an idea that a good candidate compound should specifically bind only to one target binding site. All procedures were validated by enrichment studies of a collection of 99 known HCV polymerase inhibitors and 1693 decoys. The results show that combining Glide SP with RF models provides a substantially better discrimination than the other methods in case of the validation subset-1. RF model-1 could obtain 18 known inhibitors among the 20 top ranked compounds (about 1% top ranking). However, the RF model has the limitation that it predicts well what has used for training. In the validation subset-2, only 5 known inhibitors were found among the 1% top ranked hits. Thus without prior knowledge of inhibitors, two sites docking should be considered as most suitable strategy. Within all validation sets two sites docking accurately predicts 16 known inhibitors among the 20 top ranked compounds.

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Impact of local dynamics and local interaction potentials on serine protease recognition

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Proteases are enzymes that catalyze the cleavage of peptide bonds and are important in numerous fundamental cellular processes, ranging from food digestion over blood coagulation to apoptosis. Proteases also account for 1-5% of the genome of infectious organisms such as bacteria, parasites and viruses [1].

While proteases involved in cellular signaling pathways such as the blood coagulation pathway or the apoptosis pathway show high specificity, proteases involved in processes such as the digestion of food proteins show rather low specificity. The specificity of a series of proteases has recently been quantified by Fuchs et al. through calculation of the so-called cleavage entropy as a sub-pocket-wise and overall specificity score [2] based on cleavage data from the MEROPS database [3].

To understand the mechanism of protease recognition, we will present a quantitative correlation between the local dynamics at the binding site of a series of homologous serine proteases with Trypsin-like fold obtained from molecular dynamics simulations and the specificity of the investigated proteases. In addition, we will present GRID [4] analyses for molecular dynamics trajectory snapshots to give a view of local interaction potentials at different conformational states of the proteases using selected probes. Through combination of thermodynamic data from the GRID analyses with the flexibility data obtained from molecular dynamics simulations, we want to give more insight into the interactions at protein-protein interfaces in protease recognition and discuss the contributions of enthalpic and entropic factors to protease substrate recognition.

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Theoretical Study on Silaspiropentanation Reactions of Silacyclopropylidene and Silacyclopropylidenoid

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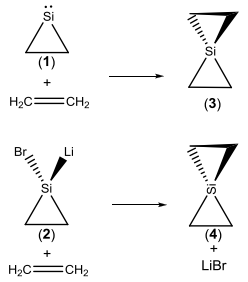
Spiropentanes are remarkable strained compounds and they are not easily accessible. Several synthesis methods are available to produce spiropentanes. More recently, Brinker et al have investigated the spiropentanation reactions via addition of *gem*-dibromocyclopropane to double bond experimentally and computationally. The synthesized spiropentane was prepared in only three steps from commercially available 1,2,4,5-tetrabromobenzene [1]. The chemistry of heterospiropentanes, compounds in which spiro carbon atom of a spiropentane has been replaced by heavier element of Si have constituted a new challenge in organometallic chemistry [2,3]. Herein, we would like to investigate the concerted silaspiropentanation reactions between singlet silacyclopropylidene(**1**)/silacyclopropylidenoid(**2**) and ethylene with the help of the Gaussian 09 program using the B3LYP theory and the cc-pVTZ basis set. The concerted reaction of silacyclopropylidenoid (**2**) with ethylene is examined. We obtained a van der Wals complex for silacyclopropylidenoid (**2**), whereas not for silacyclopropylidene (**2**). Moreover, the calculated reaction barrier for the concerted silaspiropentanation reaction mechanism of silacyclopropylidenoid is found to be 16.2 kcal/mol, but in this case the reaction is moderately endothermic, by 4.4 kcal/mol. Moreover, the calculated energy barrier of silaspiropentanation reaction between silacyclopropylidene and ethylene determined to be 3.9 kcal/mol to overcome.



Scheme 1

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Overview of modern computational methods in the research of advanced materials from bulk crystals to nanoscale structures

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In the first part of this overview we present crystal structure prediction using simulated annealing in the lead sulfide [1] and zinc oxide [2] compound, calculated using empirical potentials and on the *ab initio* level. The results were in good agreement with previous theoretical and experimental observations, and we have found some additional structure candidates as function of pressure. Next, we show results for an *ab initio* minimization data mining approach, which combines two computational methods. In this study we have investigated binary materials with elements from groups V, IV - VI, and III – VII, with the goal to identify chemical systems where recently proposed "5-5" crystal structure type might be experimentally accessible and, among others, TlF, SnO, SnS, SnSe, GeS, GeSe, PbO, PbS, ZnO and ZnS, were chosen for the study [3]. In the third part of this overview, we show calculations performed in the ZnO system using the prescribed path algorithm, where we have investigated the connectivity among experimental ZnO crystal structures on the energy landscape, and in particular transition states [4]. With the results of this study we were able to understand more about the influence of temperature in ZnO, to connect our results to the actual synthesis routes and get additional crystal and nanostructured candidates.

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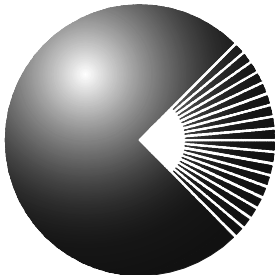

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